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(54) **Novel 7-(substituted)-8-(substituted)-9-(substituted amino)-6-demethyl-6-deoxyetracyclines as antibiotic agents**

7-Substituierte-8-substituierte-9-substituierte Amino-7-Demethyl-6-Deoxy-Tetracycline als antibiotische Mittel

6-déméthyl-6-déoxy-tétracyclines substituées en 7 et 8 et substituées en 9 par un groupe amino substitué comme agents antibiotiques

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(73) Proprietor: **American Cyanamid Company**
Madison, New Jersey 07940-0874 (US)

(72) Inventors:
- **Sum, Phaik-Eng**
  Pomona, New York 10970 (US)
- **Lee, Ving J.**
  Monsey, New York 10952 (US)
- **Hlavka, Joseph J.**
  Tuxedo Park, New York 10987 (US)
- **Testa, Raymond T.**
  Cedar Grove, New Jersey 07009 (US)

(74) Representative: **Wileman, David Francis Dr.**
c/o Patent Department
Wyeth Laboratories
Huntercombe Lane South
Taplow Maidenhead Berkshire SL6 OPH (GB)

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- **JOURNAL OF THE AMERICAN CHEMICAL SOCIETY. vol. 84 , 20 April 1962 , GASTON, PA US pages 1426 - 1430 J.J. HLAVKA ET AL. 'THE 6-DEOXYTETRACYCLINES. III. ELECTROPHILIC AND NUCLEOPHILIC SUBSTITUTION'**
- **JOURNAL OF ORGANIC CHEMISTRY. vol. 27 , October 1962 , WASHINGTON US pages 3674 - 3675 J.J. HLAVKA ET AL. 'THE 6 -DEOXYTETRACYCLINES. IV. S PHOTOCHEMICAL DISPLACEMENT OF A DIAZONIUM GROUP'**
- **JOURNAL OF MEDICINAL CHEMISTRY vol. 6 , July 1963 , WASHINGTON US pages 405 - 407 J.L. SPENCER ET AL. '6-DEOXYTETRACYCLINES. V. 7,9-DISUBSTITUTED PRODUCTS'**

EP 0 582 810 B1

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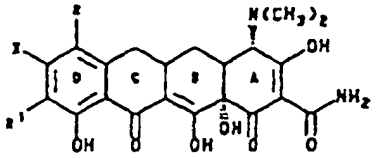
Description

[0001] The invention relates to novel [4S-(4alpha, 12aalpha)]-4-(dimethylamino)-7-(substituted)-8-(substituted)-9-(substituted)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamides herein after called 7-(substituted)-8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracyclines, which are useful as antibiotic agents and exhibit antibacterial activity against a wide spectrum of organisms including organisms which are resistant to tetracyclines.

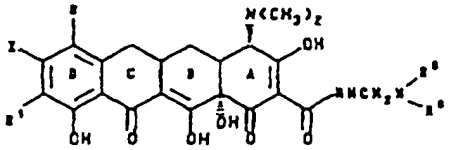
[0002] The invention also relates to novel 7-(substituted)-8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracycline intermediates useful for making the novel compounds of the present invention and to novel methods for producing the novel compounds and intermediate compounds.

SUMMARY OF THE INVENTION

[0003] This invention is concerned with novel 7-(substituted)-8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracyclines, represented by formulas I and II, which have antibacterial activity; with method of treating infectious diseases in warm blooded animals employing these new compound; with methods of treating or controlling veterinary diseases; with pharmaceutical preparations containing these compounds; with novel intermediate compounds and processes for the production of these compounds. More particularly, this invention is concerned with compounds of formulas I and II which have enhanced in vitro and in vivo antibiotic activity against tetracycline resistant strains as well as a high level of activity against strains which are normally susceptible to tetracyclines.



I



II

wherein X is selected from halogen or trifluoromethanesulfonyloxy; the halogen is selected from iodine, bromine, chlorine, or fluorine;

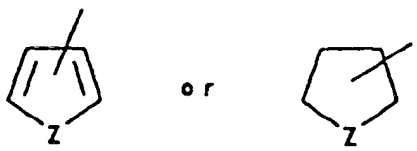
R and R^1 are the same or different and are selected from amino; halogen (selected from chlorine, bromine, fluorine or iodine); or $-NR^2R^3$;

and when R or R^1 = $-NR^2R^3$ and R^2 = methyl or ethyl; then R^3 = methyl or ethyl,

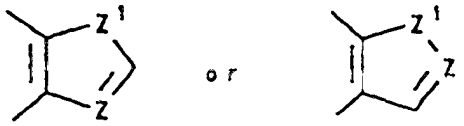
and when R or R^1 = $-NR^2R^3$ and R^2 = hydrogen, then R^3 is selected from $R^4(CH_2)_nCO-$ or R^4SO_2-;

and when R^3 = $R^4(CH_2)_nCO-$ and n=0,

R^4 is selected from hydrogen; methyl, ethyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N,. O, or S heteroatom;



Z - N, O or S or a five membered aromatic ring with two N, O or S heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 - N, O, or S

(C_1-C_4)alkoxy group; C_6-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C_1-C_4)alkyl); (C_7-C_{10})aralkyloxy group; α-aminomethyoxycarbonyl; or halomethoxycarbonyl; and when R^3 = $R^4(CH_2)_nCO$- and n=1-4

R^4 is selected from hydrogen, methyl, ethyl, phenyl, α-naphthyl or β-naphthyl;

and when R^3 = $R^4'SO_2$, R^4' is selected from methyl, ethyl. phenyl, α-naphthyl or β-naphthyl;

R^5 is selected from hydrogen, methyl, ethyl, n-propyl or 1-methylethyl;

R^6 is selected from hydrogen, methyl, ethyl, n-propoyl or 1-methylethyl; with the proviso that R^5 and R^6 cannot both be hydrogen;

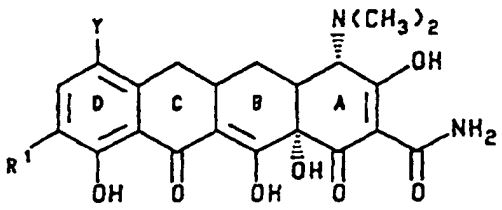
or R^5 and R^6 taken together are:

(i) -$(CH_2)_2W(CH_2)_2$-,

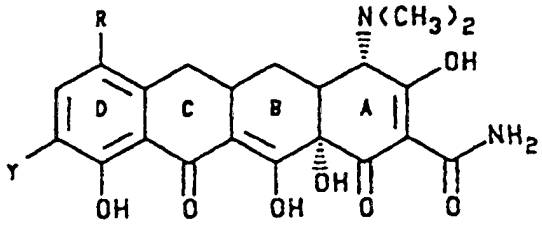
wherein W is selected from $(CH_2)_n$ and n=0-1, -NH, -N(C_1-C_3)alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen and sulfur or

(ii) substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate and pharmacologically acceptable organic and inorganic salts or metal complexes

[0004] Also included in the present invention are compounds useful as intermediates for producing the above compounds of formula I and II. Such intermediate compounds include those having the formula III and IV:



III

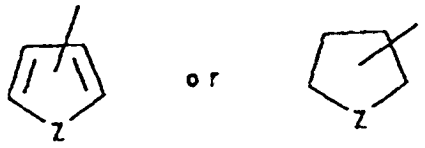


IV

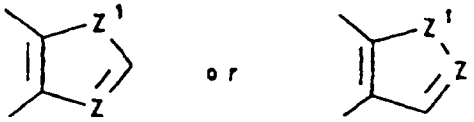
wherein Y is $-N_2^+Cl^-$ or $-N_3$;

R or R^1 are selected from nitro; amino; halogen (selected from chlorine; bromine; fluorine or iodine); cyano; hydroxy;

or -NR^2R^3;
and when R or R^1 = -NR^2R^3 and R^2 = methyl or ethyl;
R^3 = methyl or ethyl;
and when R or R^1 = -NR^2R^3 and R^2 = hydrogen,
R^3 is selected from $R^4(CH_2)_nCO$- or R^4SO_2-;
and when R^3 = $R^4(CH_2)_nCO$- and n=0,
R^4 is selected from hydrogen; methyl; ethyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, or S heteroatom optionally having a benzo or pyrido ring fused thereto:

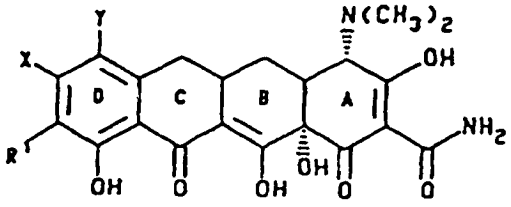


Z - N, O or S
or a five membered aromatic ring with two N, O or S heteroatoms optionally having a benzo or pyrido ring fused thereto:

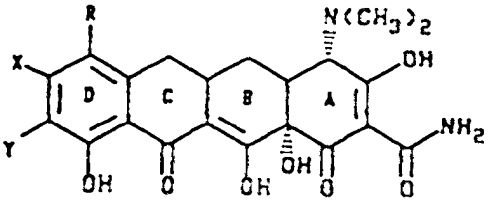


Z or Z^1 - N, O, or S
(C_1-C_4)alkoxy group; C_6-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C_1-C_4)alkyl); (C_7-C_{10})aralkyloxy group;
and when R^3 = $R^4(CH_2)_nCO$- and n=1-4,
R^4 is selected from hydrogen; methyl; ethyl; phenyl; α-naphthyl or β-naphthyl;
and when R^3 = $R^4'SO_2$- R^4' is selected from methyl; ethyl; phenyl; α-naphthyl or β-naphthyl; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

[0005] Additional intermediate compounds include those having the formula V and VI:

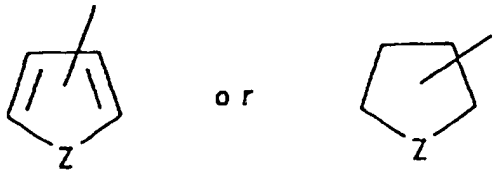


V

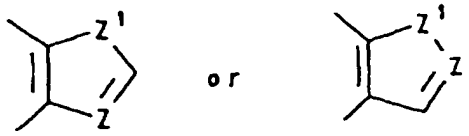


VI

wherein **X** is selected from halogen or trifluoromethanesulfonyloxy; the halogen is selected from bromine, chlorine, fluorine or iodine;
Y is selected from $-N_2^+Cl^-$ or N_3;
R or R^1 are selected from nitro; amino; halogen (selected from chlorine, bromine, fluorine or iodine); cyano; hydroxy; or $-NR^2R^3$;
and when R or R^1 = $-NR^2R^3$ and R^2 = methyl or ethyl;
R^3 = methyl or ethyl;
and when R or R^1 = $-NR^2R^3$ and R^2 = hydrogen,
R^3 is selected from $R^4(CH_2)_nCO-$ or $R^{4'}SO_2-$;
and when R^3 = $R^4(CH_2)_nCO-$ and n=0,
R^4 is selected from hydrogen; methyl, ethyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O or S heteroatom optionally having a benzo or pyrido ring fused thereto:

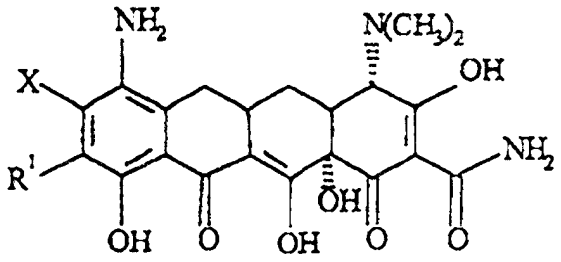


Z = N, O or S or a five membered aromatic ring with two N, O or S heteroatoms optionally having a benzo or pyrido ring fused thereto:

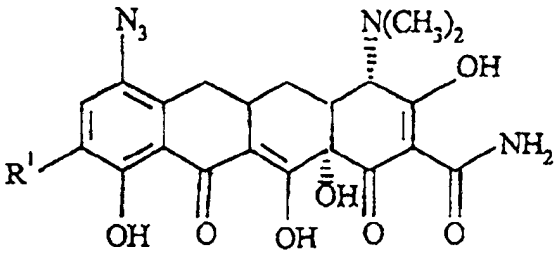


Z or Z^1 - N, O, or S
(C_1-C_4)alkoxy group; C_6-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C_1-C_4)alkyl); (C_7-C_{10})-aralkloxy group;
and when R^3 = $R^4(CH_2)_nCO-$ and n=1-4,
R^4 is selected from hydrogen, methyl, ethyl, phenyl, α-naphthyl or β-naphthyl;
and when R^3 = $R^{4'}SO_2$, $R^{4'}$ is selected from methyl, ethyl, phenyl, α-naphthyl or β-naphthyl;
and the pharmacologically acceptable organic and inorganic salts or metal complexes.

[0006] This invention also provides a method for producing a compound of the formula:

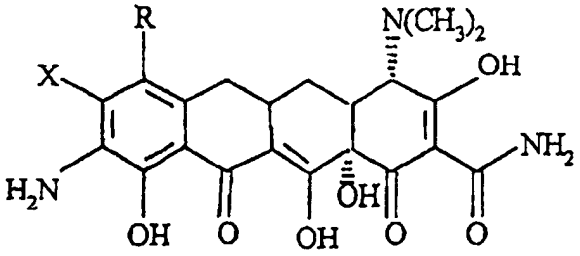


wherein X and R^1 are as herein defined which comprises reacting a compound of the formula:

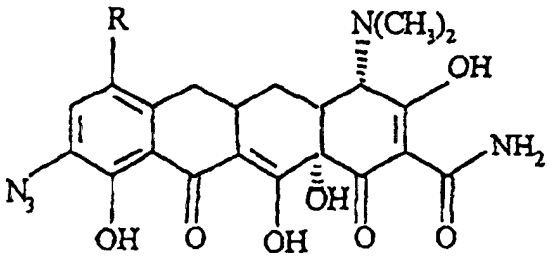


with a strong acid having the formula HX when X = halogen or trifluoromethanesulfonyloxy, to obtain the desired compound.

[0007] This invention also provides a method of producing a compound of the formula:

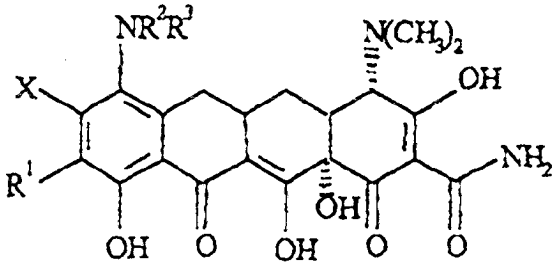


wherein X and R are as herein defined which comprises reacting a compound of the formula:

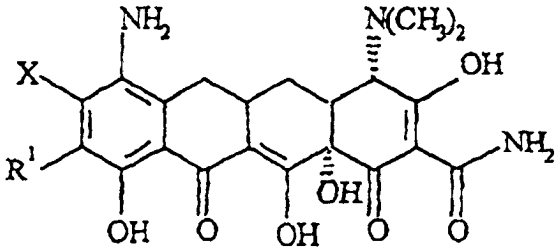


with a strong acid having the formula HX when X = halogen or trifluoromethanesulfonyloxy, to obtain the desired compound.

[0008] This invention also provides a method of producing a compound of the formula:

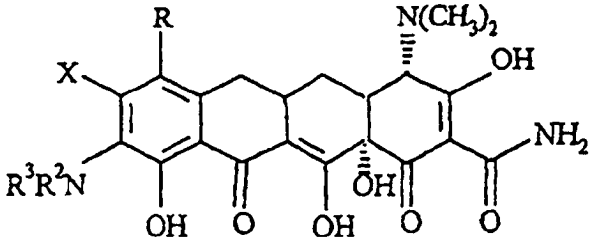


wherein X, R^1, R^2 and R^3 are as herein defined which comprises reacting a compound of the formula:

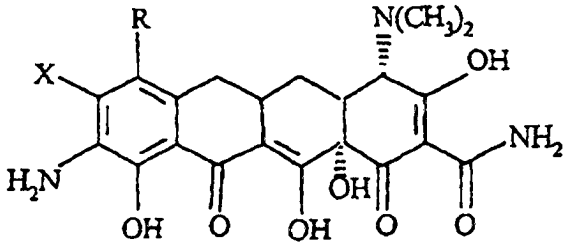


with an acyl halide of the formula R^3-halide, an acyl anhydride of the formula R^3-anhydride, a mixed acyl anhydride of the formula R^3-anhydride, a sulfonyl halide of the formula R^3-halide or sulfonyl anhydride of the formula R^3-anhydride, to obtain the desired compound.

[0009] This invention also provides a method of producing a compound of the formula:



wherein X, R, R^2 and R^3 are as herein defined which comprises reacting a compound of the formula:



with an acyl halide of the formula R^3-halide, an acyl anhydride of the formula R^3-anhydride, a mixed acyl anhydride of

the formula R^S-anhydride, a sulfonyl halide of the formula R^S-halide or sulfenyl anhydride of the formula R^S-anhydride, to obtain the desired compound.

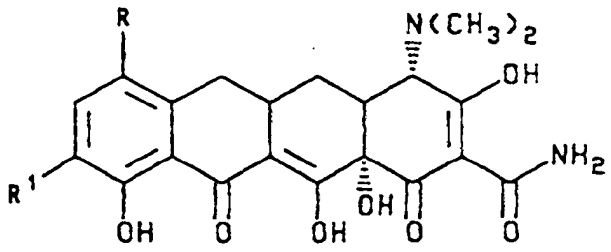
[0010] Also provided is a pharmaceutical composition comprising a compound of formula I or II or a pharmacologically acceptable organic or inorganic salt or metal complex thereof in association with a pharmaceutically acceptable carrier.

[0011] Also provided is use of a compound of formula I or II as defined herein in the preparation of a medicament for the prevention, treatment or control of bacterial infections in warm-blooded animals.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0012] The novel compounds of the present invention may be readily prepared in accordance with the following schemes.

[0013] The starting 7-azido-9-(substituted)-6-demethyl-6-deoxytetracyclines or 9-azido-7-(substituted)-6-demethyl-6-deoxytetracyclines described in formula 1 or the salts thereof are prepared by procedures known to those skilled in the art including those described in J. J. Hlavka, et al., J. Am. Chem. Soc., 84, 1426(1962).

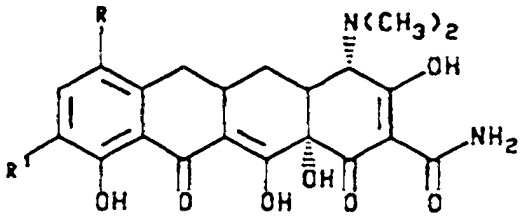


1

1a. $R^1 = N_3$ and $R = NR^2R^3$, $R^2 = R^3$
1b. $R^1 = N_3$ and $R = NR^2R^3$, $R^2 \neq R^3$
1c. $R = N_3$ and $R^1 = NR^2R^3$, $R^2 = R^3$
1d. $R = N_3$ and $R^1 = NR^2R^3$, $R^2 \neq R^3$
1e. $R^1 = N_3$ and R = X, X = halogen, hydrogen
1f. $R = N_3$ and R^1 = X, X = halogen, hydrogen

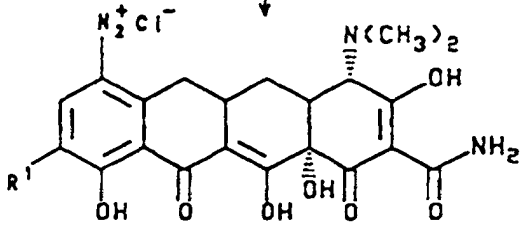
[0014] The starting 7-azido-9-(substituted)-6-demethyl-6-deoxytetracycline, 1, or 9-azido-7-(substituted)-6-demethyl-6-deoxytetracycline, 1', described in formula 1 is prepared according to Scheme 1 or Scheme 2.

Scheme 1



2

(1)

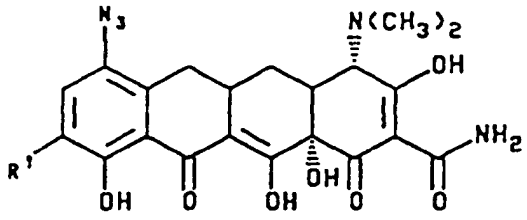


3

(2)

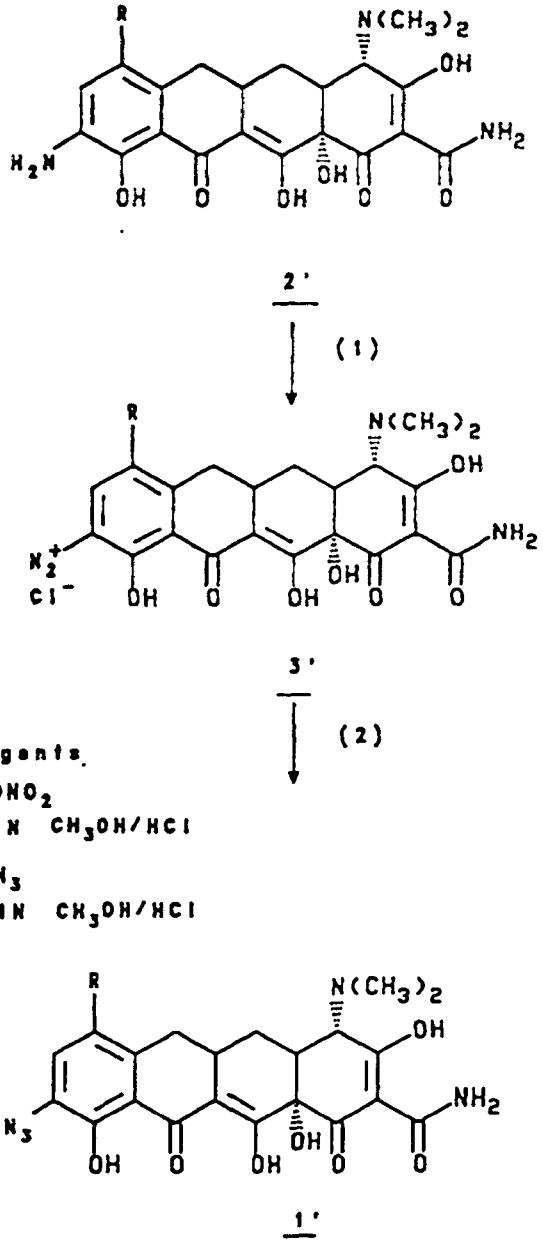
Reagents

1. $BuONO_2$
   0.1N CH_3OH/HCl
2. NaN_3
   0.1N CH_3OH/HCl



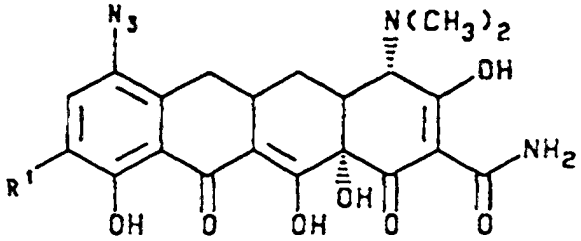
1

Scheme 2



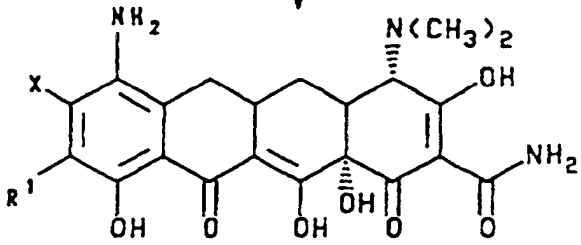
[0015] In accordance with Scheme 1 or 2, a 7-amino-9-(substituted)-6-demethyl-6-deoxytetracycline 2, or 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline 2', or their mineral acid or halide salt, dissolved in 0.1N methanolic hydrogen chloride, is treated with an excess of n-butyl nitrite to give a 7-diazonium-9-(substituted)-6-demethyl-6-deoxytetracycline, 3, or 9-diazonium-7-(substituted)-6-demethyl-6-deoxytetracycline, 3', or their mineral acid or halide salt. The formed diazonium compound, 3 or 3', or their mineral acid or halide salt, dissolved in 0.1 N methanolic hydrogen chloride, is treated with one equivalent of sodium azide to give the corresponding 7-azido-9-(substituted) -6-demethyl-6-deoxytetracycline, 1, or 9-azido-7-(substituted)-6-demethyl-6-deoxytetracycline, 1', or their mineral acid or halide salt.

Scheme 3



1

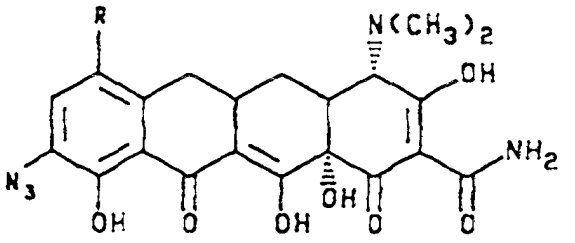
(1)



4

1. Strong acid
(HCl, H_2SO_4, CF_3SO_3H, CH_3SO_3H, HI, HF and HBr)

Scheme 4



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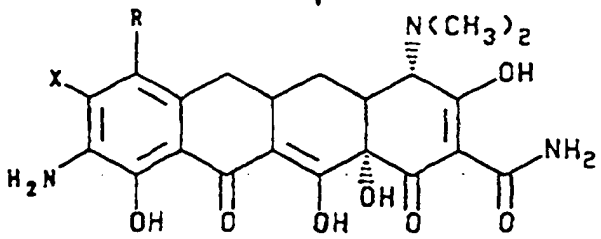


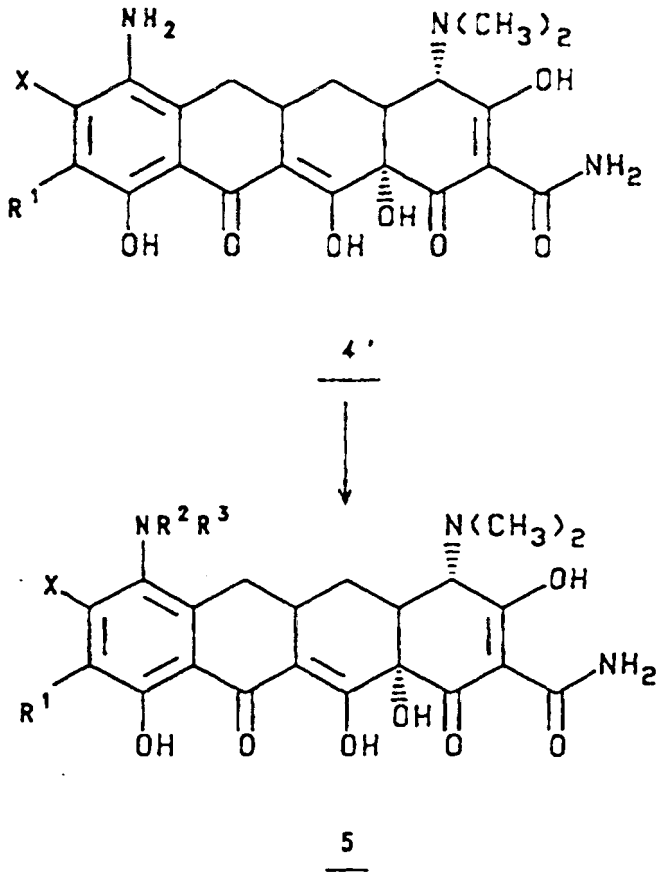
4'

1. Strong acid
(HCl, H_2SO_4, CF_3SO_3H, CH_3SO_3H, HI, HF and HBr)

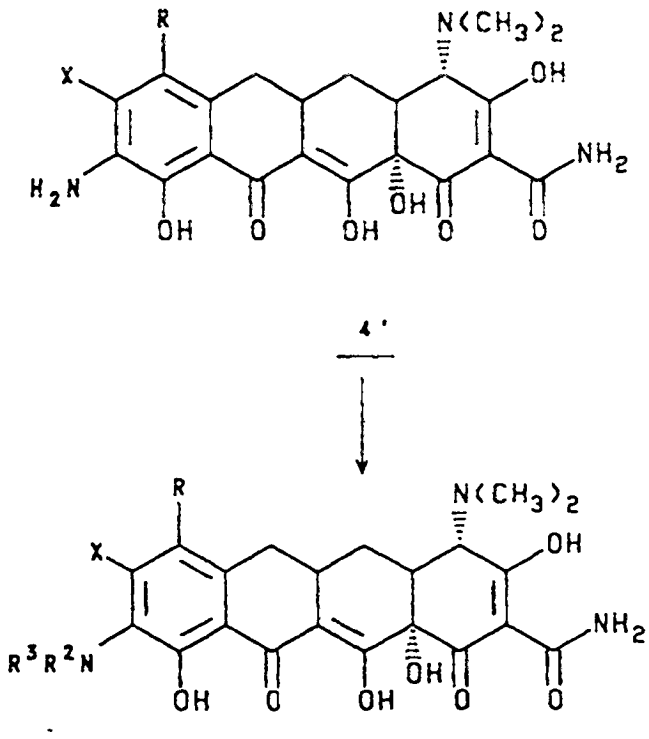
[0016] In accordance with Scheme 3 or 4, a 7-azido-9-(substituted)-6-demethyl-6-deoxytetracycline, 1, or 9-azido-7-(substituted)-6-demethyl-6-deoxytetracycline, 1', or their mineral acid or halide salt, is treated with a strong acid, such as sulfuric acid, hydrochloric acid, methanesulfonic acid, trifluoro-methanesulfonic acid, hydrobromic, hydroiodic, or hydrogen fluoride to produce a 7-amino-8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracycline, 4, or 9-amino-8-(substituted)-7-(substituted)-6-demethyl-6-deoxytetracycline, 4', or their mineral acid or halide salt.

[0017] The 7-amino-8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracycline, 4, or 9-amino-8-(substituted)-7-(substituted)-6-demethyl-6-deoxytetracycline, 4', or their mineral acid or halide salt, can be further converted as described in Schemes 5, 6, 7 and 8.

Scheme 5


NH2
N(CH3)2
X
OH
R1
NH2
OH
O
OH
O
O
4'
NR2R3
N(CH3)2
X
OH
R1
NH2
OH
O
OH
O
O
5

Scheme 5

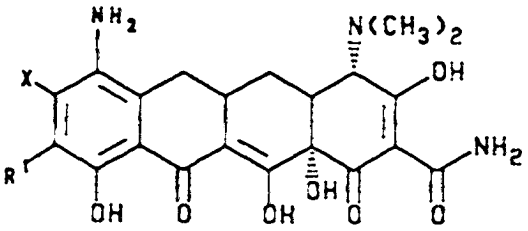


4'

5'

[0018] In accordance with Scheme 5 or 6, a 7-amino-8- (substituted) -9- (substituted) -6-demethyl-6-deoxytetracycline, 4, or a 9-amino-8-(substituted)-7-(substituted)-6-demethyl-6-deoxytetracycline, 4', or their mineral acid or halide salt, is treated with an acyl chloride, acyl anhydride, mixed acyl anhydride, sulfonyl chloride or sulfonyl anhydride in the presence of a suitable acid scavenger in a variety of solvents to form the corresponding 7-(acyl or sulfonyl amino)-8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracycline, 5, or 9-(acyl or sulfonyl amino)-8-(substituted)-7-(substituted)-6-demethyl-6-deoxytetracycline, 5' , or their mineral acid or halide salt. The acid scavenger is selected from sodium bicarbonate, sodium acetate, pyridine, triethylamine, N,O-bis(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl) trifluoroacetamide, potassium carbonate or a basic ionexchange resin. The solvents are selected from watertetrahydrofuran, N-methylpyrrolidone, 1,3-dimethyl-2-imidazolidinone, hexamethylphosphoramide, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone or 1,2-dimethoxyethane.

Scheme 7



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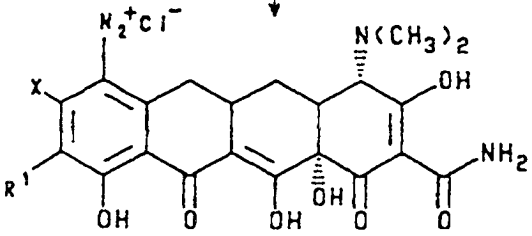

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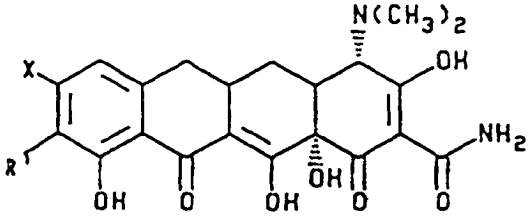
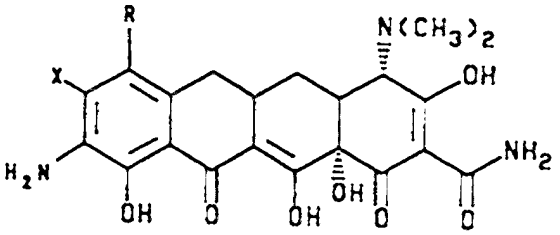


7

Scheme 8



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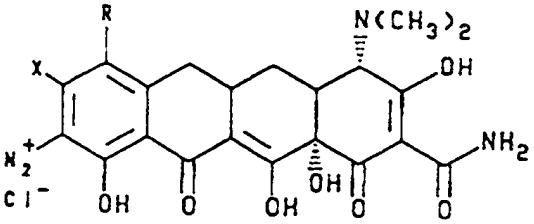
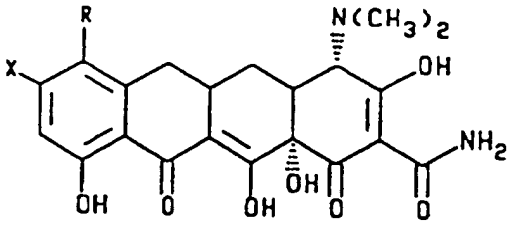


6'

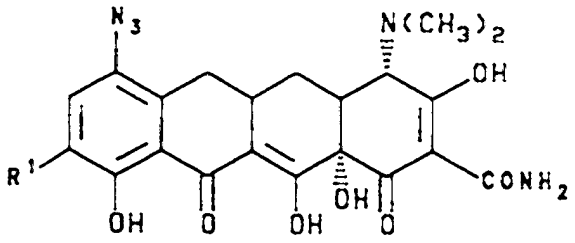


7'

[0019] In accordance with Scheme 7 or 8, a 7-amino-8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracycline, 4, or 9-amino-8-(substituted)-7-(substituted)-6-demethyl-6-deoxytetracycline, 4', or their mineral acid or halide salt, is converted to the respective diazonium salt, 6 or 6', using procedures known to those skilled in the art including those described in J. J. Hlavka, et al., J. Am. Chem. Soc., 84, 1420(1962).

[0020] The diazonium salts, 6 or 6', are reduced to their respective 8-(substituted)-7-(substituted)-6-demethyl-6-deoxytetracycline, 7, or 8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracycline, 7', by heating in an alcohol.

Scheme 9



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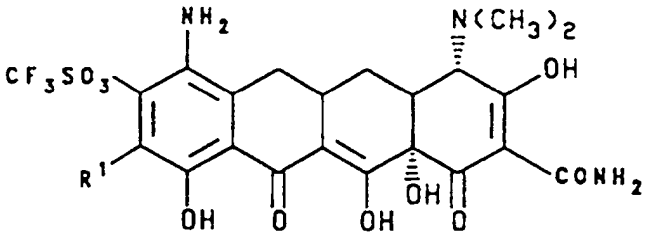
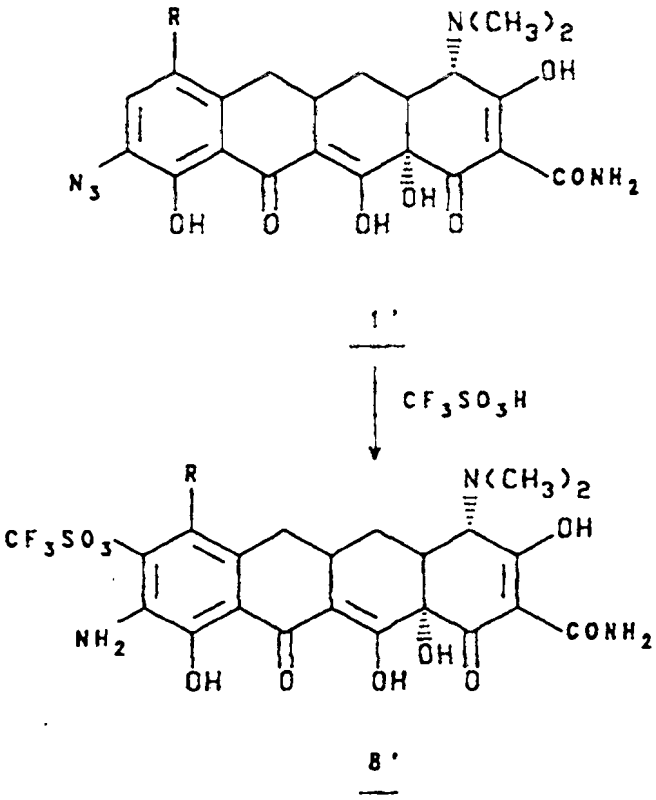


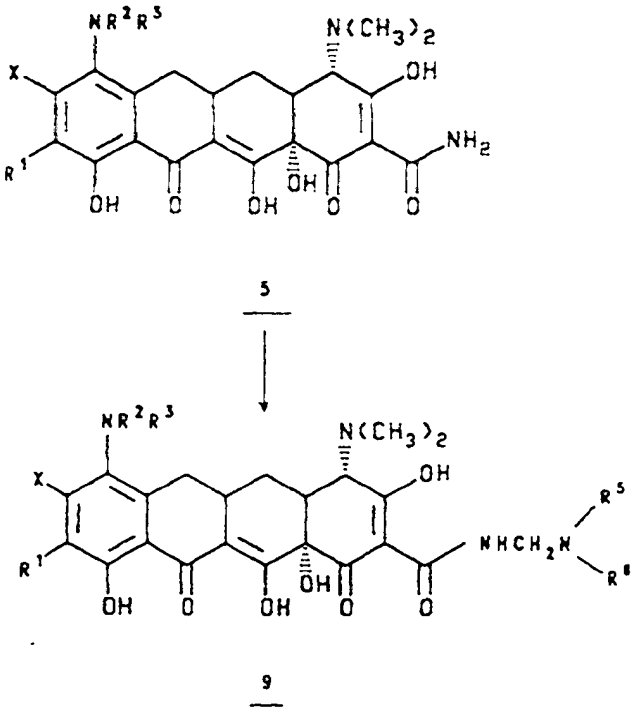
8

Scheme 10

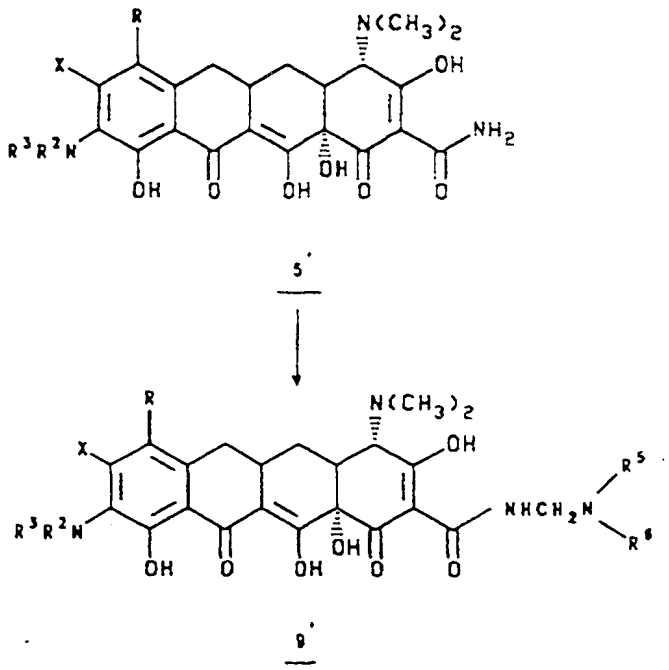


[0021] In accordance with Scheme 9 or 10, a 7-azido-9-(substituted)-6-demethyl-6-deoxytetracycline, 1, or a 9-azido-7-(substituted)-6-demethyl-6-deoxytetracycline, 1', is treated with trifluoromethanesulfonic acid to give the desired 7-amino-9-(substituted)-8-(trifluoromethanylsulfonyloxy)-6-demethyl-6-deoxytetracycline, 8, or 9-amino-7-(substituted)-8-(trifluoromethanylsulfonyloxy)-6-demethyl-6-deoxytetracycline, 8'.

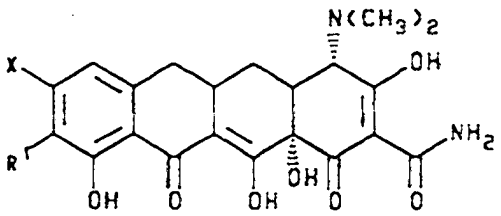
Scheme 11


NR2R3
N(CH3)2
X
OH
R1
NH2
OH
O
OH
O
O
OH
5
NR2R3
N(CH3)2
X
OH
R1
NHCH2N
R5
R6
OH
O
OH
O
O
OH
9

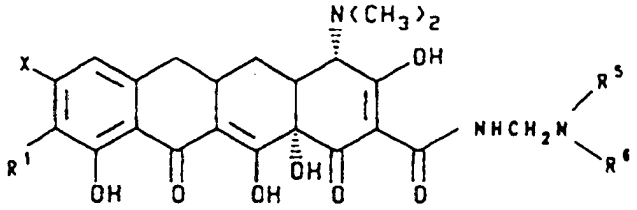
Scheme 12


R
X
N(CH3)2
OH
R3R2N
NH2
OH
O
OH
OH
O
O
5'
R
X
N(CH3)2
OH
R3R2N
NHCH2N
R5
R6
OH
O
OH
OH
O
O
8'

Scheme 13

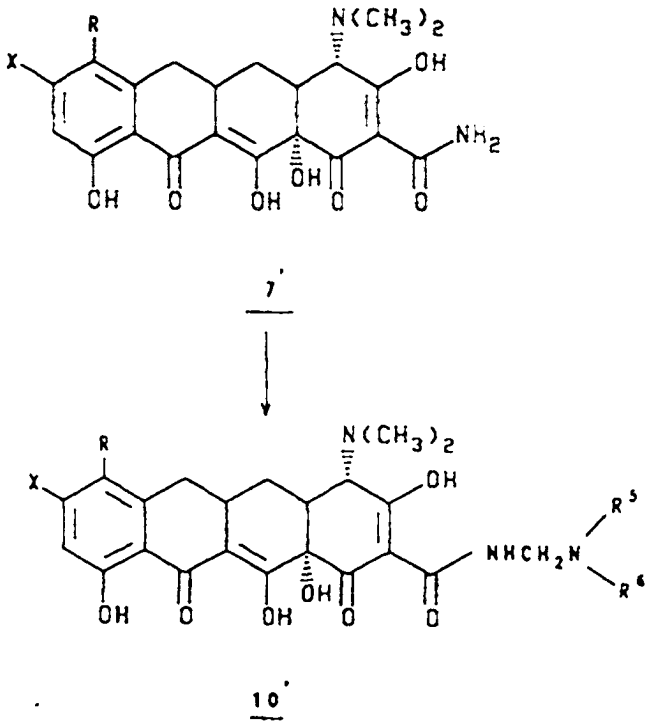


7



10

Scheme 14



7'

10'

[0022] In accordance with Schemes 11-14, Compounds 5, 5', 7, or 7' are selectively N-alkylated in the presence of formaldehyde and either a primary amine such as methylamine, ethylamine, benzylamine, methyl glycinate, (L or D) lysine, (L or D)alanine or their substituted congeners; or a secondary amine such as morpholine, pyrrolidine, piperidine or their substituted congeners to give their corresponding Mannich base adduct, 9, 9', 10, or 10'.

[0023] The 7-(substituted)-8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracyclines may be obtained as metal complexes such as aluminum, calcium, iron, magnesium, manganese and complex salts; inorganic and organic salts and corresponding Mannich base adducts using methods known to those skilled in the art (Richard C. Larock, Comprehensive Organic Transformations, VCH Publishers, 411-415, 1989). Preferably, the 7-(substituted)-8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracyclines are obtained as inorganic salts such as hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric or sulfate; or organic salts such as acetate, benzoate, citrate, cysteine or other amino acids, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate or arysulfonate. In all cases the salt formation occurs with the C(4)-dimethylamino group. The salts are preferred for oral and parenteral administration.

BIOLOGICAL ACTIVITY

Method for in Vitro Antibacterial Evaluation (Table I)

[0024] The minimum inhibitory concentration (MIC), the lowest concentration of the antibiotic which inhibits growth of the test organism, is determined by the agar dilution method using Muller-Hinton II agar (Baltimore Biological Laboratories). An inoculum density of 1-5 x 10^5 CFU/ml and an antibiotic concentration (32-≤0.015 µg/ml) is used. The plates are incubated for 18 hours at 35°C in a forced air incubator. The test organisms comprise strains sensitive to tetracycline and genetically defined strains that are resistant to tetracycline, due to inability to bind bacterial ribosomes (tetM).

E. coli in Vitro Protein Translation System (Table II)

[0025] An in vitro, cell free, protein translation system using extracts from E. coli strain MRE 600 (tetracycline sen-

s.tive) and a derivative of MRE 600 containing the tetM determinant has been developed based on literature methods [J.M. Pratt. Coupled Transcription-translation in Prokaryotic Cell-free Systems. Transcription and Translation, a Practical Approach. (B.D. Hames and S.J. Higgins, eds) p. 179-209, IRL Press, Oxford-Washington, 1984].

[0026] Using the system described above, the tetracycline compounds of the present invention are tested for their ability to inhibit protein synthesis in vitro. Briefly, each 10 µl reaction contains S30 extract (a whole extract) made from either tetracycline sensitive cells or an isogenic tetracycline resistant (tetM) strain, low molecular weight components necessary for transcription and translation (i.e., ATP and GTP), a mix of 19 amino acids (no methionine), ^{35}S labeled methionine, DNA template (either pBR322 or pUC119), and either DMSO (control) or the novel tetracycline compound to be tested ("novel TC") dissolved in DMSO.

[0027] The reactions are incubated for 30 minutes at 37°C. Timing is initiated with the addition of the S30 extract, the last component to be added. After 30 minutes, 2.5 µl of the reaction is removed and mixed with 0.5 ml of 1N NaOH to destroy RNA and tRNA. Two to three ml of 25% trichloroacetic acid is added and the mixture incubated at room temperature for 15 minutes. The trichloroacetic acid precipitated material is collected on Whatman GF/C filters and washed with a solution of 10% trichloroacetic acid. The filters are dried and the retained radioactivity, representing incorporation of ^{35}S-methionine into polypeptides, is counted using standard liquid scintillation methods.

[0028] The percent inhibition (P.I.) of protein synthesis is determined to be:

$$P.I. = 100 - \left(\frac{\text{Retained radioactivity of novel TC containing sample}}{\text{Retained radioactivity of DMSO control reaction}} \right) \times 100$$

In Vivo Antibacterial Evaluation (Table III)

[0029] The therapeutic effects of tetracyclines are determined against an acute lethal infection with Staphylococcus aureus strain Smith (tetracycline sensitive). Female, mice, strain CD-1 (Charles River Laboratories), 20 ± 2 grams, are challenged by an intraperitoneal injection of sufficient bacteria (suspended in hog mucin) to kill non-treated controls within 24-48 hours. Antibacterial agents, contained in 0.5 ml of 0.2% aqueous agar, are administered subcutaneously or orally 30 minutes after infection. When an oral dosing schedule is used, animals are deprived of food for 5 hours before and 2 hours after infection. Five mice are treated at each dose level. The 7 day survival ratios from 3 separate tests are pooled for calculation of median effective dose (ED_{50}).

Testing Results

[0030] The claimed compounds exhibit antibacterial activity against a spectrum of tetracycline sensitive and resistant Gram-positive and Gram-negative bacteria, especially, strains of E. coli, S. aureus and E. faecalis, containing the tetM resistance determinants (Table I). Notable is 8-chloro-9-(formylamino)-4-(dimethylamino)-6-demethyl-6-deoxytetracycline, compound A in Table I, which has good in vitro activity against tetracycline resistant strains containing the tetM resistance determinant (such as S. aureus UBMS 88-5 and S. aureus UBMS 90-1 and 90-2) and is equally as effective as minocycline against tetracycline susceptible strains.

[0031] Protein synthesis, determined using cell-free extracts from the tetracycline susceptible strain MRE600, is inhibited by tetracycline, minocycline and the 8-chloro-9-(formylamino)-4-(dimethylamino)-6-demethyl-6-deoxytetracycline of this invention (Table II). Protein synthesis, determined using cell-free extracts from strain MRE600 (tetM), is resistant to tetracycline and minocycline, since less than 20% inhibition is achieved even at 1mg/ml concentration of minocycline vs 90% inhibition at 0.3mg/ml of the tetracycline sensitive ribosome extracts prepared from strain MRE600 (Table II). In contrast, 8-chloro-9-(formylamino)-4-(dimethylamino)-6-demethyl-6-deoxytetracycline effectively inhibited protein synthesis in extracts prepared from either MRE600 or MRE600 (tetM) (Table II). The evidence presented indicates that 8-chloro-9-(formylamino)-4-(dimethylamino)-6-demethyl-6-deoxytetracycline is an inhibitor of protein synthesis at the ribosome level. The ability of 8-chloro-9-(formylamino)-4-(dimethylamino)-6-demethyl-6-deoxytetracycline to inhibit bacterial growth almost certainly reflects directed inhibition of bacterial protein synthesis. Therefore, it is expected to exhibit a bacteriostatic effect against susceptible bacteria, as is the case with other tetracyclines.

[0032] The antibacterial activity of 8-chloro-9-(formylamino)-4-(dimethylamino)-6-demethyl-6-deoxytetracycline is also demonstrated by in vivo efficacy in animals infected with S. aureus Smith (Table III).

[0033] The improved efficacy of 8-chloro-9-(formylamino)-4-(dimethylamino)-6-demethyl-6-deoxytetracycline is demonstrated by the in vitro activity against isogenic strains into which the resistance determinants, such as tetM, were cloned (Table I); the inhibition of protein synthesis by tetM ribosomes (Table II); and the in vivo activity against experimental infections (Table III).

LETTER	NAME
A	8-Chloro-4-(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride or sulfate
B	8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5-5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate
C	7-Amino-8-chloro-4-(dimethylamino)-1,4-4a,5,5a,6,11,12a-octahydro-3,10,12,12a tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide hydrochloride
D	8-(Aminocarbonyl)-2-chloro-10-(dimethylamino)-5,6a,10,10a,11,11a,12-octahydro-5,7-dioxo-1-naphthacenediazonium. (Comparative compound)
E	8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6-11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate
F	8-Chloro-4,7-bis(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate
G	9-Amino-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
H	9-Amino-8-chloro-4,7-(dimethylamino)-1,4 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate
I	[7S-(7alpha, 10aalpha)]-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6-6a,7,10,10a, 12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-carbamic acid methyl ester
J	[4S-(4alpha, 12aalpha)]-8-Chloro-4-(dimethylamino)-9-hydrazino-1,4,4a,5,5a,6-11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride
K	Tetracycline hydrochloride
L	Minocycline hydrochloride
M	[4S(4alpha,12aalpha)]-9-Amino-8-chloro-7-(diethylamino)-4-dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Table I

ANTIBACTERIAL ACTIVITY OF 8-(HALOGEN)-7-(SUBSTITUTED)-9-(SUBSTITUTED)-6-DEMETHYL-6-DEOXYTETRACYCLINES
MIC(ug/ml)

Organism	Compound											
	A	B	C	D	E	F	G	H	I	J	K	L
E. coli UBMS 88-1 (tetB)	32	>32	>32	>32	>32	>32	>32	>32	>32	32	>32	16
E. coli UBMS 88-2 (sensitive)	0.12	8	2	32	16	1	4	8	NT	2	0.25	0.25
E. coli UBMS 89-1 (tetM)	NG	>32	32	32	16	0.5	NG	NG	8	16	16	8
E. coli UBMS 89-2 (sensitive)	0.25	16	4	32	16	1	4	16	16	4	1	1
E. coli ATCC 25922	0.12	8	2	16	8	0.25	1	4	8	1	0.5	0.5
S. aureus UBMS 88-4 (sensitive)	<0.015	0.03	0.5	0.5	0.25	0.12	<0.015	0.12	0.06	0.06	0.12	0.03
S. aureus UBMS 88-5 (tetM)	0.12	0.5	32	4	2	0.25	1	1	0.5	0.5	>32	4
S. aureus UBMS 88-7 (tetK)	16	0.5	>32	8	4	4	2	0.25	2	1	>32	0.12
S. aureus UBMS 90-1 (tetM)	0.25	0.05	32	4	2	0.5	1	2	0.5	0.5	>32	4

NG = No growth
NT = Not tested

EP 0 582 810 B1

Table I (Cont'd.)

ANTIBACTERIAL ACTIVITY OF 8-(HALOGEN)-7-(SUBSTITUTED)-9-(SUBSTITUTED)-6-DEMETHYL-6-DEOXYTETRACYCLINES
MIC(ug/ml)

Organism	Compound											
	A	B	C	D	E	F	G	H	I	J	K	L
S. aureus UBMS 90-3 (sensitive)	<0.015	0.06	0.12	0.5	0.12	0.06	<0.015	0.12	0.06	0.03	0.06	0.03
S. aureus UBMS 90-2 (tetM)	0.03	0.5	8	2	1	0.12	0.25	0.5	0.5	0.5	32	4
S. aureus IVES 2943 (meth. resistant)	32	1	>32	16	4	8	8	1	4	2	>32	4
S. aureus SMITH (MP) (sensitive)	<0.015	0.06	0.25	0.5	0.12	0.06	<0.015	0.06	0.06	0.03	0.06	0.03
S. aureus IVES 1983 (MP) (meth. resistant)	32	1	>32	16	4	8	8	4	4	2	>32	4
S. aureus ATCC 29213 (sensitive)	<0.015	≤0.015	0.12	0.12	0.03	0.06	<0.015	<0.015	≤0.015	≤0.015	≤0.015	≤0.015
Enteroc. spp. 12201	0.5	1	32	2	1	0.5	2	4	2	0.05	32	8
S. faecal. ATCC 29212	<0.015	1	8	2	2	0.06	0.25	0.5	0.5	0.5	16	1
S. haemol. AVAH 88-3	NT	0.25	1	1	0.5	0.12	0.12	0.12	0.5	0.25	1	0.12

NG = No growth
NT = Not tested

EP 0 582 810 B1

TABLE II

INHIBITION OF PROTEIN SYNTHESIS BY E. COLI CELL-FREE RIBOSOMES WITH TETRACYCLINES			
Compound	Conc.	% Inhibition	
		Wild Type S30	tetM S30
H	1.0 mg/ml	57	29
	0.3 mg/ml	62	21
	0.1 mg/ml	52	19
L	1.0 mg/ml	90	19
	0.3 mg/ml	91	0
	0.1 mg/ml	66	0
A	1.0 ml/ml	93	NT
	0.3 mg/ml	98	NT
NT = Not Tested			

TABLE III

PROTECTIVE ACTIVITY IN MICE INFECTED WITH STAPHYLOCOCCUS AUREUS SMITH	
Compound	ED_{50} (mg/kg)
H	4-8
B	>16
M	>16
A HCL	4-8
A H_2SO_4	4-8
J	>16

[0034] When the compounds are employed as antibacterials, they can be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

[0035] An effective amount of compound from 2.0 mg/kg of body weight to 100.0 mg/kg of body weight should be administered one to five times per day via any typical route of administration including but not limited to oral, parenteral (including subcutaneous, intravenous, intramuscular, intrasternal injection or infusion techniques), topical or rectal, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0036] These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

[0037] The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds

is preferred.

[0038] These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0039] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and fluid. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

[0040] The invention will be more full described in conjunction with the following specific examples which are not to be construed as limiting the scope of the invention. Examples 1, 7, 13 and 16 illustrate the preparation of starting materials.

Example 1

[7S-(7alpha, 10alpha)]-9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12-dioxo-2-naphthacenediazonium chloride sulfate (1:1) **[Formula III wherein R=-N(CH_3)$_2$, X=H, R^1= -N_2^+ Cl^-]**

[0041] To a O°C solution of 3.0 g of 9-amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate dissolved in 100 ml of 0.1N methanolic hydrogen chloride is added, dropwise, 6.6 ml of butyl nitrite. The reaction is stirred at O°C for 1 hour, poured into 400 ml of diethyl ether, collected and dried to give 2.64 g of the desired product. MS(FAB): m/z 484 (M + H)

Example 2

[4S-(4alpha, 12aalpha)]-9-Azido-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11, dioxo-2-naphthacenecarboxamide hydrochloride (1:1) **[Formula III wherein R=-N(CH_3)$_2$, X=H, R^1= -N_3]**

[0042] To a room temperature solution of 2.64 g of product from Example 1 dissolved in 84 ml of 0.1N methanolic hydrogen chloride is added 0.353 g of sodium azide. The mixture is stirred at room temperature for 4 hours, poured into 500 ml of diethyl ether and collected to give 2.5 g of the desired product. IR(KBr): 2080 cm^{-1}.

Example 3

[4S-(4α,12aα)]-9-Amino-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2naphthacenecarboxamide sulfate**[Formula I wherein R=-N(CH_3)$_2$, X=Cl, R^1= -NH_2]**

[0043] One gram of product from Example 2 is added to 10 ml of O°C concentrated sulfuric acid. The reaction is stirred at O°C for 1.5 hours, poured into 500 ml of diethyl ether, collected and dried to give 1.1 g of the desired product. MS(FAB): m/z 507 (M + H).

Example 4

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1) **[Formula I wherein R=-N(CH_3)$_2$, X=Cl, R^1=-NR^2R^3 where R^2 = H and R^3 is $R^4(CH_2)_nCO$ where n = 0 and R^4 = H]**

[0044] To a O°C solution of 0.092 g of product from Example 3 dissolved in 5.0 ml of 98% formic acid is added 0.0164 g of sodium acetate. The resulting mixture is stirred at O°C for 10 minutes, followed by the addition of 0.23 ml of acetic anhydride. The reaction is stirred at room temperature of 1 hour, poured into diethyl ether and collected to give 0.045 g of solid. The collected solid is triturated with 50 ml of ethyl acetate and filtered. The filtrate is concentrated in vacuo to give 0.019 g of the desired product. MS(FAB): m/z 535 (M + H).

Example 5

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-3,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1) **[Formula I wherein R=-N(CH$_3$)$_2$, X=Cl, R^1=H]**

[0045] To a O°C solution of 0.090 g of product from Example 3 dissolved in 35 ml of 0.1N methanolic hydrogen chloride is added 0.2 ml of butyl nitrite. The reaction is stirred at room temperature for 1 hour, poured into 70 ml of diethyl ether and collected give 0.070 g of the desired diazonium chloride intermediate.

[0046] A solution of 0.070 g of the above intermediate dissolved in 20 ml of methyl alcohol is heated at the reflux temperature for 45 minutes, poured into diethyl ether and collected to give 0.056 g of the desired product. MS(FAB): m/z 491 (M$^+$).

Example 6

[4S-(4α,12aα)]-7-Amino-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride (1:1) **[Formula I wherein R=-NH$_2$, X=Cl, R^1=H]**

[0047] Three grams of 7-azido-6-demethyl-6-deoxytetracycline hydrochloride, prepared by the procedure described in J. Am. Chem. Soc., 84:1426-1430. is added to 120 ml of cold concentrated hydrochloric acid and stirred for 1 3/4 hours at ice bath temperature. The reaction mixture is concentrated in vacuo to give 2.9 g of the desired product. MS (FAB):m/z 464 (M + H).

Example 7

[6aS-(6aα,10aα)]-8-(Aminocarbonyl)-2-chloro-10-(dimethylamino)-5,6a,10,10a,11,11a,12-octahydro 4,6,6a, 9-tetrahydroxy-5,7-dioxo-1-naphthacenediazonium chloride hydrochloride **[Intermediate wherein R=-N$_2^H$ Cl, X= Cl, R^1= H]**

[0048] To a O°C solution of 0.50 g of product from Example 6 dissolved in 15 ml of 0.1N methanolic hydrogen chloride is added 1.0 ml of butyl nitrite. The reaction is stirred at 0°C for 1 hour, poured into 500 ml of diethyl ether and collected to give 0.48 g of the desired product. IR(KBr): 2200 cm^{-1}.

Example 8

[4S-(4alpha, 12aalpha)]-7-Azido-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride **[Intermediate wherein R=-N3, X= Cl, R^1= H]**

[0049] To a room temperature solution of 0.48 g of product from Example 7 dissolved in 20 ml of 0.1N methanolic hydrogen chloride is added 0.055 g of sodium azide. The reaction mixture is stirred at room temperature for 4 hours, poured into 100 ml of diethyl ether and collected to give 0.366 g of the desired product. MS(FAB): m/z 490 (M + H)

Example 9

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride (1:1) **[Formula I wherein R=-H, X=Cl, R^1=H]**

[0050] To a O°C solution of 0.095 g of product from Example 6 dissolved in 5 ml of 0.1N methanolic hydrogen chloride is added 0.3 ml of butyl nitrite. The reaction mixture is stirred at OoC for 1 hour, poured into diethyl ether and collected to give 0.070 g of the desired intermediate.

[0051] A solution of 0.050 g of the above intermediate dissolved in 15 ml of methyl alcohol is heated at the reflux temperature for 1 hour and concentrated in vacuo to give 0.035 g of the desired product. MS(FAB): m/z 449 (M + H).

Example 10

[4S-(4α,12aα)]-9-Amino-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride (1:1) **[Formula I wherein R=-H, X=Cl, R^1=NH$_2$]**

[0052] To 10 ml of concentrated hydrochloric acid at O°C is added 0.20 g of 9-azido-6-demethyl-6-deoxytetracycline

hydrochloride prepared by the procedure described in J. Am. Chem. Soc., 84: 1426-1430. The reaction is stirred at O°C for 1 1/2 hours and concentrated in vacuo to give 0.195 g of the desired product. MS(FAB): m/z 464 (M + H).

Example 11

[4S-(4α,12aα)]-8-Chloro-4-(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride (1:1) **[Formula I wherein R=-H, X=Cl, R^1=NR^2R^3 where R^2=H and R^3=$R^4(CH_2)_nCO$ where n=0 and R^4 = hydrogen, HCl salt]**

[0053] To a O°C solution of 0.103 g of product from Example 10, as the hydrochloride, dissolved in 6 ml of 98% formic acid is added 0.23 ml of acetic anhydride. The resulting mixture is stirred O°C for 5 minutes followed by 1 hour at room temperature. The reaction is poured into 500 ml of diethyl ether and collected to give 0.090 g of the desired product. MS(FAB): m/z 492 (M + H).

Example 12

[4S-(4α,12aα)]-7-Amino-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-iodo-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1) **[Intermediate wherein R=-NH_2, X=H, R^1=I]**

[0054] To a O°C solution of 0.285 g of 7-amino-6-demethyl-6-deoxytetracycline dissolved in 5 ml of concentrated sulfuric acid is added 1.2 equivalents of N-iodosuccinimide. The reaction is stirred at O°C for 15 minutes then poured into 400 ml of diethyl ether. The resulting solid is collected and dried to give 0.23 g of the desired product. ^{1}H NMR (DMSO-d_6): δ8.0 (C-8 H).

Example 13

[6aS-(6aalpha, 10aalpha)]-8-(Aminocarbonyl)-10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-3-iodo-5,7-dioxo-1-naphthacene-diazonium chloride sulfate (1:1:1) **[Formula IV wherein R=-N2, Cl-X=H, R^1=I]**

[0055] To a O°C solution of 0.15 g of product from Example 12 dissolved in sufficient 0.1N methanolic hydrogen chloride to affect solution is added, dropwise, 0.143 ml of n-butyl nitrite. The reaction is stirred at 0°C for 30-45 minutes then poured into cold, stirring diethyl ether. The resulting solid is collected, washed with diethyl ether and dried to give 0.12 g of the desired product. ^{1}H NMR(DMSO-d_6): δ8.52 (C-8 H).

Example 14

[4S-(4alpha, 12aalpha)]-7-Azido-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-hydroxy-9-iodo-1,11-dioxo-2-naphthacenecarboxamidesulfate (1:1) **[Formula IV wherein R=-N_3, X=H, R^1=I]**

[0056] The title compound is prepared by the procedure of Example 8, using 2.2 g of product from Example 13, 60 ml of 0.1N methanolic hydrogen chloride and 0.203 g of sodium azide to give (after purification) 0.65 g of the desired product. IR(KBr): 2100 cm -1. MS(FAB): m/z 582 (M + H).

Example 15

[4S-(4alpha, 12aalpha)]-7-Amino-8-chloro-4-(di-methylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-iodo-1,11-dioxo-2-naphthacene-carboxamide sulfate (1:1) **Formula I wherein R=-NH_2, X=Cl, R^1=I]**

[0057] A mixture of 0.2 g of product from Example 14 and 1 ml of concentrated hydrochloric acid is stirred at room temperature for 2 hours. The reaction mixture is triturated with iso-propanol and ether, collected and dried to give 0.18 g of the desired product. MS(FAB): m/z 590 (M + H).

Example 16

[7S-(7alpha, 10aalpha)]-9-(Aminocarbonyl)-4-(diethyl-amino)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenediazonium chloride sulfate (2:1) **[Formula III wherein R=-N(Et)$_2$, X=H, R^1=-N$_2$H Cl$^-$ = NH]**

[0058] To a O°C solution of 1.85 g 9-amino-7(diethylamino)-6-demethyl-6-deoxytetracycline, prepared by the procedure described in U.S. Patent Application Serial No. 07/771,697, filed October 4, 1991 dissolved in 40 ml of 0.1N methanolic hydrogen chloride is added 1.85 ml of n-butyl nitrite. The reaction mixture is stirred at O°C for 2 hours, poured into diethyl ether, the solid is collected and washed with diethyl ether to give 2.1 g of the desired product. ^{1}H NMR(DMSO-d$_6$): δ7.9 (C-8 H).

Example 17

[4S-(4alpha, 12aalpha)]-9-Azido-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide disulfate **[Formula III wherein R=-N(Et)$_2$, X=H, R^1=N$_3$]**

[0059] To a room temperature solution of 1.192 g of product from Example 16 dissolved in 75 ml of 0.1N methanolic hydrogen chloride is added 0.104 g of sodium azide. The reaction is stirred at room temperature for 2 hours, poured slowly into diethyl ether and collected to give 0.8 g of the desired product. ^{1}H NMR(DMSO-d$_6$): δ7.5 (C-8 H).

Example 18

[4S-(4alpha, 12aalpha)]-9-Azido-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamidedihydrochloride**[Formula III wherein R=-N(Et)$_2$, X=H, R^1=N$_3$]**

[0060] To a room temperature solution of 0.6 g of product from Example 17 dissolved in water is added solid sodium acetate to achieve pH 5. The mixture is extracted 2 times with chloroform, the organic layer is dried over sodium sulfate and concentrated in vacuo. The residue is redissolved in 5 ml of methanol and 2 drops of concentrated hydrochloric acid is added. The reaction solution is then added dropwise to 120 ml of diethyl ether. The resulting solid is collected to give 0.4 g of the desired product. IR(KBr): 2100 cm^{-1}.

Example 19

[4S-(4alpha, 12aalpha)]-9-Amino-8-chloro-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphtha-cenecarboxamide sulfate **[Formula III wherein R=-N(Et)$_2$, X=Cl, R^1=NH$_2$]**

[0061] A mixture of 0.23 g of product from Example 18 and 5 ml of concentrated hydrochloric acid is stirred at room temperature for 2 hours. The resulting solid is triturated with isopropanol and diethyl ether. The solid is collected, washed with diethyl ether and dried to give 0.21 g of the desired product. MS(FAB): m/z 535 (M + H).

Example 20

[7S-(7alpha, 10aalpha)]-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]carbamic acid methyl ester**[Formula I wherein R=H, X=Cl, R^1=-NHCO$_2$CH$_3$ R^1=R^4(CH$_2$)$_n$CO when n = 0 and R^4 = methoxy]**

[0062] To a room temperature solution of 0.20 g of product from Example 10, dissolved in 4 ml of 1-methyl-2-pyrrolidinone, is added 0.30 g of sodium bicarbonate. The mixture is stirred for 5 minutes followed by the addition of 34 11 of methyl chloroformate. The reaction is stirred at room temperature for 1 hour, filtered into 200 ml of diethyl ether and collected to give 0.066 g of the desired product. MS(FAB): m/z 522 (M + H).

Example 21

[4S-(4alpha, 12aalpha)]-9-Amino-4,7-bis(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamidehydrochloride **[Formula I wherein R=N(CH_3)$_2$, X=F, R^1=NH_2]**

[0063] The title compound is prepared by the procedure of Example 3, using the product from Example 2 and liquid hydrogen fluoride.

Example 22

[6aS-(6aalpha, 10alpha)]-3-Amino-8-(aminocarbonyl)-10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6a,9-tetrahydroxy-5,7-dioxo-2-naphthacenyl ester trifluoromethanesulfonic acid **[Formula I wherein R=H, X=-OSO_2CF_3, R^1= -NH_2]**

[0064] The title compound is prepared by the procedure of Example 3, using 9-azido-6-demethyl-6deoxytetracycline prepared by the procedure described in J. Am. Chem. Soc., 84:1426-1430 and trifluoro-methanesulfonic acid.

Example 23

[4S-(4alpha, 12aalpha)]-9-Amino-4-(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamidehydrochloride**[Formula I wherein R=H, X=F, R^1=-NH_2]**

[0065] The title compound is prepared by the procedure of Example 21, using 9-azido-6-demethyl-6deoxytetracycline prepared by the procedure described in the above reference.

Example 24

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-8-fluoro-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12-12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamidehydrochloride **[Formula I wherein R=H, X=F, R^1=-NHCHO]**

[0066] The title compound is prepared by the procedure of Example 4, using the product from Example 23.

Example 25

[4S-(4alpha, 12aalpha)]-4-(Dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamidehydrochloride **[Formula I wherein R=H, X=F, R^1=H]**

[0067] The title compound is prepared by the procedures described in Examples 1 and 5, using the product from Example 23.

Example 26

[4S-(4alpha, 12alpha)]-4,7-Bis(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-hydroxy-1,11-dioxo-2-naphthacenecarboxamide **[Formula I wherein R=N(CH_3)$_2$, X=F, R^1=H]**

[0068] The title compound is prepared by the procedure of Example 5, using the product of Example 21.

Example 27

[7S-(7alpha, 10aalpha)]-[9-(Aminocarbonyl)-7-(dimethylamino)-3 fluoro-5,5a,6,6a,7,10,10a,12-octahydro-1,8-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]carbamic acid methyl ester **[Formula I wherein R=H, X=F, R^1=-NR^2R^3 where R^2 is hydrogen and R^3 is $R^4(CH_2)_nCO$ where n = 0 and R^4 is methoxy]**

[0069] The title compound is prepared by the procedure of Example 20, using the product from Example 24.

Example 28

[6aS-(6aalpha, 10alpha)]-3-Amino-8-(aminocarbonyl)-1,10-bis(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-2-naphthacenyl ester trifluoromethanesulfonic acid **[Formula I wherein R=$N(CH_3)_2$, X=-O-SO_2CF_3, R^1=NH_2]**

[0070] The title compound is prepared by the procedure of Example 3, using the product from Example 3 and trifluoromethanesulfonic acid.

Example 29

[4S-(4alpha, 12aalpha)]-7-Amino-4-(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamidehydrochloride **[Formula I wherein R=$N(CH_3)_2$, X=-O-SO_2CF_3, R^1=NH_2]**

[0071] The title compound is prepared by the procedure of Example 3, using 7-azido-6-demethyl-6deoxytetracycline prepared by the procedure described in J. Am. Chem. Soc., 84:1426-1430 and liquid hydrogen fluoride at -30°C.

Example 30

[4S-(4alpha,12aalpha)]-8-Chloro-7-(diethylamino)-4-(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate **[Formula I wherein R=-$N(Et)_2$, X=Cl, R^1=-NR^2R^3 where R^2 is H and R^3 = $R^4(CH_2)_nCO$ where n is 0 and R^4 is H]**

[0072] The title compound is prepared by the procedure of Example 4, using the product from Example 19.

Example 31

[6aS-(6aalpha, 10alpha)]-[8-(Aminocarbonyl)-2-chloro-10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-1-naphthacenyl]-carbamic acid methyl ester **[Formula I wherein R=-NR^2R^3 where R^2 = H and R^3 = $R^4(CH_2)$nCO where n =O and R^4 = methoxy, X=Cl, R^1=H]**

[0073] The title compound is prepared by the procedure of Example 20, using the product from Example 6.

Example 32

[4S-(4α,12aα)]-4-(Dimethylamino)-8-fluoro-7-(formylamino)-1,4,4a,5,-5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride **[Formula I wherein R=-NR^2R^3 where R^2 = H and R^3 = $R^4(CH_2)_nCO$ wherein n = 0, and R^4 = H; X=F, R^1=H]**

[0074] The title compound is prepared by the procedure of Example 4, using the product from Example 8.

Example 33

[7S-(7alpha,10aalpha)]-[9-(Aminocarbonyl)-7-(dimethyl-amino)-3-fluoro-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-carbamic acid methyl ester **[Formula I wherein R=H, X=F, R^1 is -NR^2R^3 where R^2 = H and R^3 = $R^4(CH_2)_nCO$ where n = 0 and R^4 = methoxy]**

[0075] The title compound is prepared by the procedure of Example 20, using the product from Example 23.

Example 34

[6S-(6aalpha,10alpha)]-8-(Aminocarbonyl)-10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-3-[(methoxycarbonyl)amino]-5,7-dioxo-2-naphthacenyl ester trifluoromethanesulfonic acid **[Formula I wherein R=H, X=-OSO_2CF_3, R^1=NR^2R^3 where R^2 = H and R^3 = $R^4(CH_2)_nCO$ where n = 0 and R^4 = methoxy]**

[0076] The title compound is prepared by the procedure of Example 20, using the product from Example 22.

Example 35

[4S- (4α,12aα)]-9-Amino-8-bromo-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide (1:1) **[Formula I wherein R=H, X=Br, R^1=NH_2]**

[0077] The title compound is prepared by the procedure of Example 3, using 9-azido-6-demethyl-6-deoxytetracycline prepared by the procedure described on J. Am. Chem. Soc., 84:1426-1430 and a solution of hydrogen bromide in acetic acid (30 wt%).

Example 36

[4S-(4α,12aα)]-9-Amino-8-bromo-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamine hydrobromide **[Formula I wherein R=-$N(CH_3)_2$, X=Br, R^1=-NH_2]**

[0078] The title compound is prepared by the procedure of Example 3, using the product from Example 2 and a solution of hydrogen bromide in acetic acid (30 wt%).

Example 37

[4S-(4alpha,12aalpha)]-9-Amino-4,7-bis(dimethylamino)-8-iodo-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamidehydroiodide**[Formula I wherein R=-$N(CH_3)_2$, X=I, R^1=-NH_2]**

[0079] The title compound is prepared by the procedure of Example 3, using the product from Example 2 and hydroiodic acid.

Example 38

[4S-(4alpha,12aalpha)]-9-Amino-4-(dimethylamino)-8-iodo-1,4,4a,5,5a,11,12,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamidehydroiodide **[Formula I wherein R=H, X=I, R^1=-NH_2]**

[0080] The title compound is prepared by the procedure of Example 3, using 9-azido-6-demethyl-6-deoxytetracycline prepared by the procedure described on J. Am. Chem. Soc., 84:1426-1430 andhydroiodic acid.

Example 39

[7S-(7alpha,10aalpha)]-[9-(Aminocarbonyl)-7-(dimethyl-amino)-3-iodo-5,5a,6,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]carbamicacid methyl ester **[Formula I wherein R=H, X=I, R^1=-NR^2R^3 where R^2 = H and R^3 = $R^4(CH_2)_nCO$ where n = 0 and R^4 = methoxy]**

[0081] The title compound is prepared by the procedure of Example 20, using the product from Example 38.

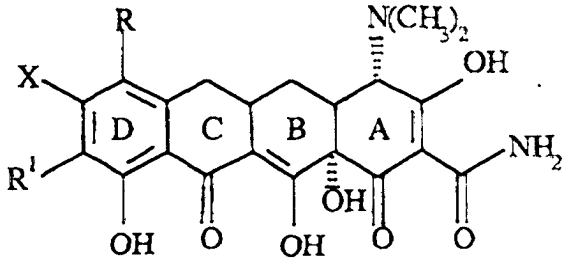
Example 40

[7S-(7alpha,10aalpha)]-[9-(Aminocarbonyl)-3-bromo-7-(dimethylamino)-5,5a,6,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]carbamicacid methyl ester **[Formula I wherein R=H, X=Br, R^1=-NR^2R^3 where R^2 = H and R^3 = $R^4(CH_2)_nCO$ where n = 0 and R^4 = methoxy]**

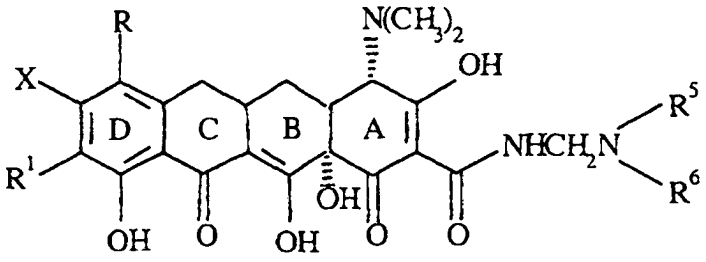
[0082] The title compound is prepared by the procedure of Example 20, using the product from Example 35.

Claims

1. A compound of the formula I or II:



I



II

wherein:

X is selected from trifluoromethylsulfonyloxy; iodine; bromine; chlorine; and fluorine;

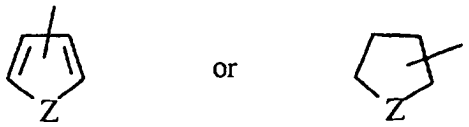
R and R^1 are the same or different and are selected from amino; chlorine; bromine; fluorine; iodine; and $-NR^2R^3$;

and when R or R^1 = NR^2R^3 and R^2 = methyl or ethyl; then R^3 = methyl or ethyl,

and when R or R^1 = $-NR^2R^3$ and R^2 = hydrogen, then R^3 is selected from $R^4(CH_2)_nCO-$ or $R^4'SO_2-$;

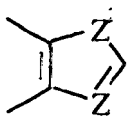
where when R^3 = $R^4(CH_2)_nCO-$ and n=0,

R^4 is selected from hydrogen; methyl; ethyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O or S heteroatom

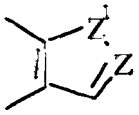


Z = N, O or S

or a five membered aromatic ring with two N, O or S heteroatoms optionally having a benzo or pyrido ring fused thereto:



or



Z or Z^1 = N, O, or S

$(C_1$-$C_4)$ alkoxy group;

C_6-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo and $(C_1$-$C_4)$ alkyl);

$(C_7$-$C_{10})$ aralkyloxy group;

α-aminomethoxycarbonyl;
or

halomethoxycarbonyl;

and when $R^3 = R^4(CH_2)_nCO$- and n=1-4,

R^4 is selected from hydrogen; methyl, ethyl; phenyl, α-naphthyl or β-naphthyl;

and when $R^3 = R^{4'}SO_2$-

$R^{4'}$ is selected from methyl, ethyl; phenyl, α-naphthyl or β-naphthyl;

R^5 is selected from hydrogen, methyl, ethyl,n-propyl or 1-methyethyl;

R^6 is selected from hydrogen, methyl, ethyl, n-propyl or 1-methylethyl;

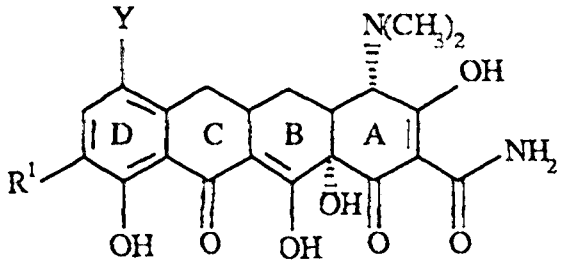
with the proviso that R^5 and R^6 cannot both be hydrogen;

or R^5 and R^6 taken together are

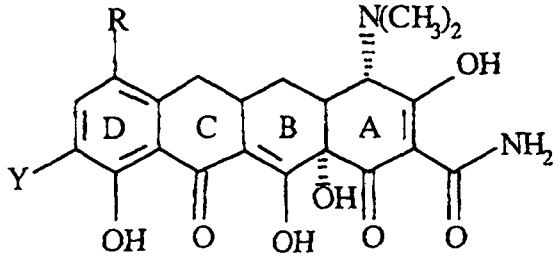
(i) $-(CH_2)_2W(CH_2)_2$-, wherein W is selected from $(CH_2)_n$ and n=0-1, -NH, $-N(C_1$-$C_3)$alkyl [straight or branched], $-N(C_1$-$C_4)$ alkoxy, oxygen and sulfur;
or
(ii) substitued congeners selected from (L or D)proline and ethyl-(L or D)prolinate;

and pharmacologically acceptable organic and inorganic salts or metal complexes.

2. A compound of the formula III or IV:



III



IV

wherein Y is $-N_3$;

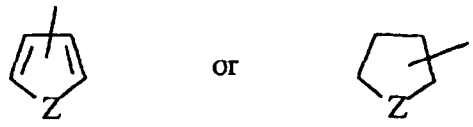
R or R^1 are selected from nitro; amino; chlorine; bromine; fluorine; iodine; cyano; hydroxy and $-NR^2R^3$;

and when R or R^1 = $-NR^2R^3$ and R^2 = methyl or ethyl,then R^3 = methyl or ethyl,

and when R or R^1 = $-NR^2R^3$ and R^2 = hydrogen, then R^3 is selected from $R^4(CH_2)_nCO-$ or R^4SO_2-;

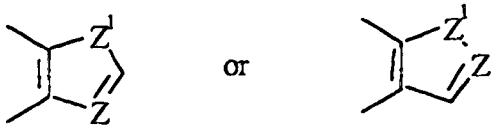
where when R^3 = $R^4(CH_2)_nCO-$ and n=0,

R^4 is selected from hydrogen; methyl, ethyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O or S heteroatom optionally having a benzo or pyrido ring fused thereto:



Z = N, O or S

or a five membered aromatic ring with two N, O or S heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, or S
(C_1-C_4) alkoxy group;
C_6-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C_1-C_4) alkyl); or
(C_7-C_{10}) aralkyloxy group;

and when $R^3 = R^4(CH_2)_nCO$- and n=1-4,

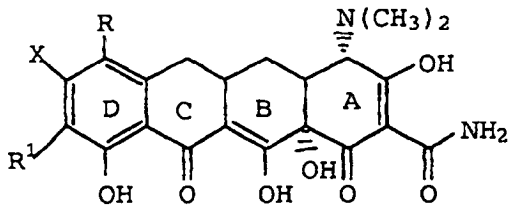
R^4 is selected from hydrogen; methyl; ethyl; phenyl; α-naphthyl or β-naphthyl;

and when $R^3 = R^{4'}SO_2$-

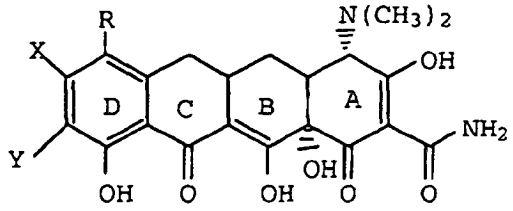
$R^{4'}$ is selected from methyl, ethyl, phenyl, α-naphthyl or β-naphthyl;

and the pharmacologically acceptable organic and inorganic salts or metal complexes.

3. A compound of the formula V or VI:



V



VI

wherein X is selected from trifluoromethylsulfonyloxy; bromine; chlorine; fluorine and iodine;

Y is selected from $-N_2^+Cl^-$ or $-N_3$;

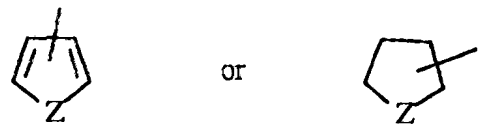
R or R^1 are selected from nitro; amino; chlorine; bromine; fluorine; iodine; cyano; hydroxy and $-NR^2R^3$;

and when R or $R^1 = NR^2R^3$ and R^2 = methyl or ethyl; then R^3 = methyl or ethyl,

and when R or $R^1 = -NR^2R^3$ and R^2 = hydrogen, then R^3 is selected from $R^4(CH_2)_nCO$- or $R^{4'}SO_2$-;

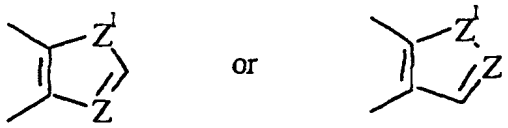
where when $R^3 = R^4(CH_2)_nCO$- and n=0,

R^4 is selected from hydrogen; methyl, ethyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O or S heteroatom optionally having a benzo or pyrido ring fused thereto:



Z – N, O or S

or a five membered aromatic ring with two N, O or S heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, or S

(C_1-C_4) alkoxy group;

C_6-aryloxy group selected from phenoxy or substituted phenoxy (substitution selected from halo, (C_1-C_4) alkyl); or

(C_7-C_{10}) aralkyloxy group;

and when $R^3 = R^4(CH_2)_nCO$- and n=1-4,

R^4 is selected from hydrogen; methyl, ethyl; phenyl, α-naphthyl or β-naphthyl ;

and when $R^3 = R^{4'}SO_2$- and n=0,

$R^{4'}$ is selected from methyl, ethyl, phenyl, α-naphthyl or β-naphthyl;

and the pharmacologically acceptable organic and inorganic salts or metal complexes.

4. A compound according to Claim 1, which is one of the following:

[4S-(4α,12aα)]-8-Chloro-4,7-bis(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1);
[Formula I wherein R=-N(CH_3)$_2$, X=Cl, R^1=-NR^2R^3 where R^2 = H and R^3 is $R^4(CH_2)_nCO$ where n = 0 and R^4 = H]

[4S-(4α,12aα)]-9-Amino-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate;
[Formula I wherein R=-N(CH_3)$_2$, X=Cl, R^1= -NH_2]

[4S-(4α,12aα)]-7-Amino-8-chloro-4-(dimethylamino)-1,4,-4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-iodo-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1);
[Formula I wherein R=-NH_2, X=Cl, R^1=I]

[4S-(4α,12aα)]-9-Amino-8-chloro-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate;
[Formula III wherein R=-N(Et)$_2$, X=Cl, R^1=NH_2]

[4S-(4α,12aα)]-9-Amino-4,7-bis-(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride;
[Formula I wherein R=N(CH_3)$_2$, X=F, R^1=NH_2]

[6aS-(6aα,10α)]-3-Amino-8-(aminocarbonyl)-1,10-bis(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-

4,6,6a,9-tetrahydroxy-5,7-dioxo-2-naphthacenyl ester trifluoro-methanesulfonic acid;
[Formula I wherein R=N(CH$_3$)$_2$, X=-O-SO$_2$CF$_3$, R^1=NH$_2$]

[4S-(4α, 12aα)]-8-Chloro-7-(diethylamino)-4-(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate.
[Formula I wherein R=-N(Et)$_2$, X=Cl, R^1=-NR^{2}R^3 where R^2 is H and R^3 = R^4(CH$_2$)$_n$CO where n is 0 and R^4 is H]

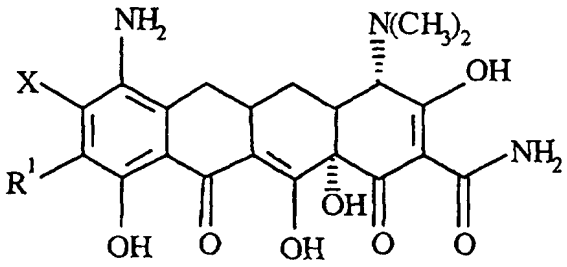
[4S-(4α,12aα)]-9-Amino-8-bromo-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamine hydrobromide:
[Formula I wherein R=-N(CH$_3$)$_2$, X=Br, R^1=-NH$_2$]
or

[4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-8-iodo-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydroiodide;
[Formula I wherein R=-N(CH$_3$)$_2$, X=I, R^1=-NH$_2$]

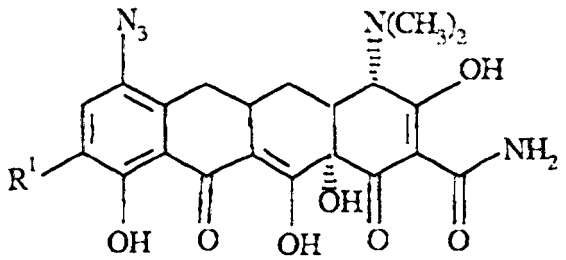
5. A compound according to Claim 2, which is one of the following:

[4S-(4α,12aα)]-9-Azido-7-bis(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride (1:1);
[Formula III wherein R=-N(CH$_3$)$_2$, X=H, R^1= -N$_3$]
[4S-(4α,12aα)]-9-Azido-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide disulfate;
[Formula III wherein R=-N(Et)$_2$, X=H, R^1=N$_3$]
[4S-(4α,12aα)]-9-Azido-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride,
[Formula III wherein R=-N(Et)$_2$, X=H, R^1=N$_3$]
or
[4S-(4α,12aα)]-7-Azido-4-(dimethylamino)-1,4,4a,5,5a,6,-11,12a-octahydro-3,10,12,12a tetrahydroxy-9-iodo-1,11-dioxo-2-naphthacenecarboxamide sulfate (1:1).
[Formula IV wherein R=-N$_3$, X=H, R^1=I]

6. A method of producing a compound of the formula:

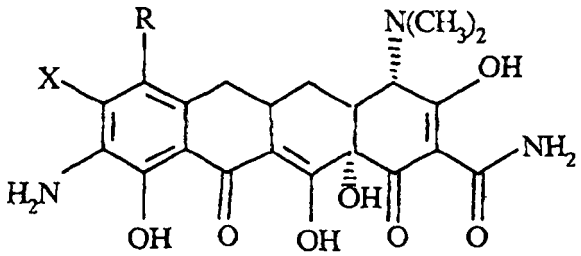


wherein X and R^1 are as defined in Claim 1;
which comprises reacting a compound of the formula:

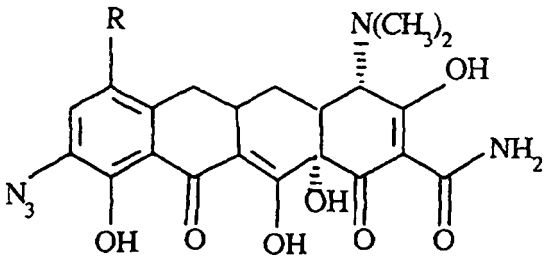


with a strong acid having the formula HX when X – halogen or trifluoromethanesulfonyloxy, to obtain the desired compound.

7. A method of producing a compound of the formula:

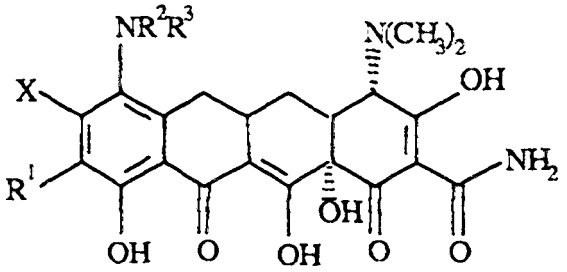


wherein X and R are as defined in Claim 1;
which comprises reacting a compound of the formula:

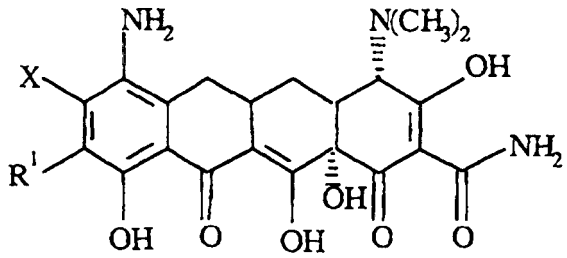


with a strong acid having the formula HX when X = halogen or trifluoromethanesulfonyloxy, to obtain the desired compound.

8. A method of producing a compound of the formula:

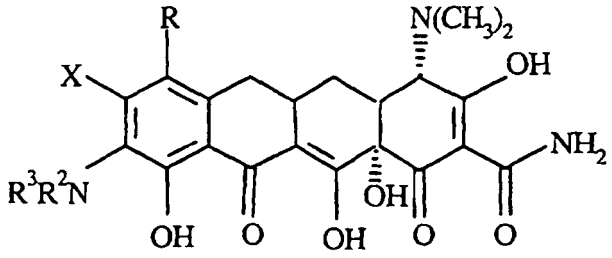


wherein X, R^1, R^2 and R^3 are as defined in Claim 1;
which comprises reacting a compound of the formula:

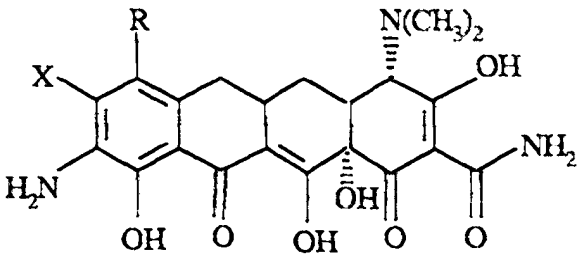


with an acyl halide of the formula R^3-halide, an acyl anhydride of the formula R^3-anhydride, a mixed acyl anhydride of the formula R^3-anhydride, a sulfonyl halide of the formula R^3-halide or sulfonyl anhydride of the formula R^3-anhydride, to obtain the desired compound.

9. A method of producing a compound of the formula:



wherein X, R, R^2 and R^3 are as defined in Claim 1;
which comprises reacting a compound of the formula:



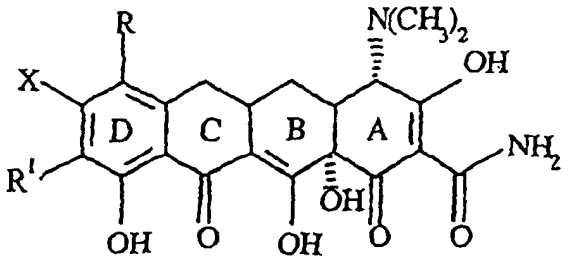
with an acyl halide of the formula R^3-halide, an acyl anhydride of the formula R^3-anhydride, a mixed acyl anhydride of the formula R^3-anhydride, a sulfonyl halide of the formula R^3-halide or sulfonyl anhydride of the formula R^3-anhydride, to obtain the desired compound.

10. Use of a compound of formula I or II as claimed in Claim 1 or Claim 4 in the preparation of a medicament for the prevention, treatment or control of bacterial infections in warm-blooded animals.

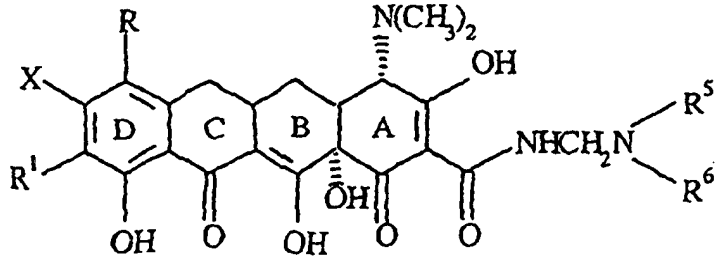
11. A pharmaceutical composition comprising a compound according to Claim 1 or Claim 4 in association with a pharmaceutically acceptable carrier.

Patentansprüche

1. Verbindung der Formel I oder II:



I



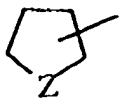
II,

worin:

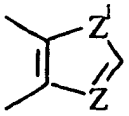
X ausgewählt wird aus Trifluormethylsulfonyloxy; Iod; Brom; Chlor und Fluor;
R und R^1 gleich oder unterschiedlich sind und ausgewählt werden aus Amino; Chlor; Brom, Fluor; Iod und

$-NR^2R^3$;
und wenn R oder $R^1 = NR^2R^3$ und R^2 = Methyl oder Ethyl; dann R^3 = Methyl oder Ethyl;
und wenn R oder $R^1 = -NR^2R^3$ und R^2 = Wasserstoff, dann wird R^3 ausgewählt aus $R^4(CH_2)_nCO-$ oder $R^4'SO_2-$;
worin wenn $R^3 = R^4(CH_2)_nCO-$ und n = 0,
R^4 ausgewählt wird aus Wasserstoff; Methyl; Ethyl; einer heterocyclischen Gruppe, ausgewählt aus einem fünfgliedrigen aromatischen oder gesättigten Ring mit einem N-, O- oder S-Heteroatom

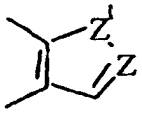
oder



Z = N, O oder S
oder einem fünfgliedrigen aromatischen Ring mit zwei N-, O- oder S-Heteroatomen, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyridoring:



oder

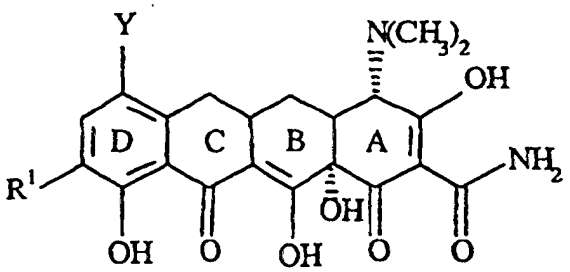


Z oder Z^1 = N, O oder S
(C_1-C_4)-Alkoxy-Gruppe;
C_6-Aryloxy-Gruppe, ausgewählt aus Phenoxy oder substituiertem Phenoxy (Substitution ausgewählt aus Halogen und (C_1-C_4)-Alkyl);
(C_7-C_{10})-Aralkyloxy-Gruppe;
α-Aminomethoxycarbonyl; oder
Halogenmethoxycarbonyl;
und wenn $R^3 = R^4(CH_2)_nCO-$ und n = 1-4, R^4 ausgewählt wird aus Wasserstoff; Methyl; Ethyl; Phenyl, α-Naphthyl oder β-Naphthyl;
und wenn $R^3 = R^4'SO_2-$, R^4' ausgewählt wird aus Methyl, Ethyl; Phenyl, α-Naphthyl oder β-Naphthyl;
R^5 ausgewählt wird aus Wasserstoff, Methyl, Ethyl, n-Propyl oder 1-Methylethyl;
R^6 ausgewählt wird aus Wasserstoff, Methyl, Ethyl, n-Propyl oder 1-Methylethyl;
unter der Voraussetzung, dass R^5 und R^6 nicht beide Wasserstoff darstellen können;
oder R^5 und R^6 zusammengenommen für

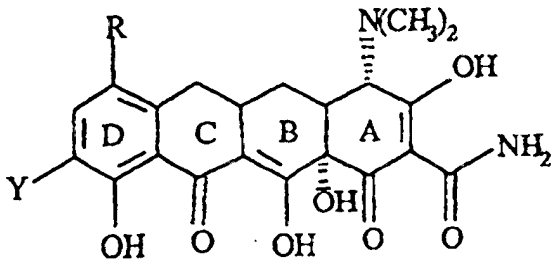
(i) $-(CH_2)_2W(CH_2)_2-$ stehen, worin W ausgewählt wird aus $(CH_2)_n$ und n = 0-1; -NH, $-N(C_1-C_3)$Alkyl [grade oder verzweigt], $-N(C_1-C_4)$-Alkoxy, Sauerstoff und Schwefel stehen; oder
(ii) substituierte Gleichartige stehen, ausgewählt aus (L- oder D-)Prolin und Ethyl-(L- oder D-)-prolinat;

und pharmakologisch annehmbare organische und anorganische Salze oder Metallkomplexe.

2. Verbindung der Formel III oder IV:

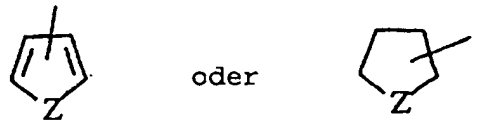


III

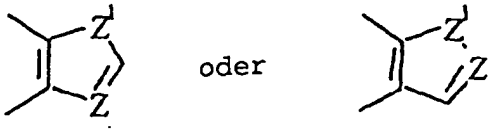


IV,

worin Y für $-N_3$ steht;
R oder R^1 ausgewählt werden aus Nitro; Amino; Chlor; Brom, Fluor; Iod, Cyano; Hydroxy und $-NR^2R^3$;
und wenn R oder $R^1 = -NR^2R^3$ und R^2 = Methyl oder Ethyl; dann R^3 = Methyl oder Ethyl,
und wenn R oder $R^1 = -NR^2R^3$ und R^2 = Wasserstoff, dann wird R^3 ausgewählt aus $R^4(CH_2)_nCO-$ oder $R^{4'}SO_2-$;
worin wenn $R^3 = R^4(CH_2)_nCO-$ und n = 0,
R^4 ausgewählt wird aus Wasserstoff; Methyl; Ethyl; einer heterocyclischen Gruppe, ausgewählt aus einem fünfgliedrigen aromatischen oder gesättigten Ring mit einem N-, O- oder S-Heteroatom, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyridoring:



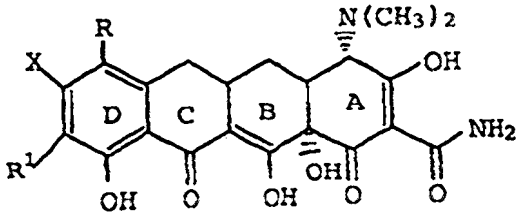
Z = N, O oder S oder einem fünfgliedrigen aromatischen Ring mit zwei N-, O- oder S-Heteroatomen, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyridoring:



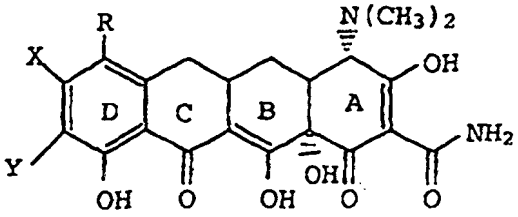
Z oder Z^1 = N, 0 oder S
(C_1-C_4)-Alkoxy-Gruppe;
C_6-Aryloxy-Gruppe, ausgewählt aus Phenoxy oder substituiertem Phenoxy (Substitution ausgewählt aus Halogen, (C_1-C_4)-Alkyl); oder
(C_7-C_{10})-Aralkyloxy-Gruppe;
und wenn $R^3 = R^4(CH_2)_nCO-$ und n = 1-4, R^4 ausgewählt wird aus Wasserstoff; Methyl; Ethyl; Phenyl, α-Naphthyl oder β-Naphthyl;
und wenn $R^3 = R^{4'}SO_2-$, $R^{4'}$ ausgewählt wird aus Methyl. Ethyl: Phenyl. α-Naphthyl oder β-Naphthyl;

und die pharmakologisch annehmbaren organischen und anorganischen Salze oder Metallkomplexe.

3. Verbindung der Formel V oder VI:

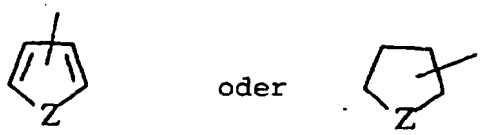


V



VI,

worin X ausgewählt wird aus Trifluormethylsulfonyloxy; Brom; Chlor; Fluor und Iod;
Y ausgewählt wird aus $-N_2^+Cl^-$ oder $-N_3$;
R oder R^1 ausgewählt werden aus Nitro; Amino; Chlor; Brom, Fluor; Iod; Cyano; Hydroxy und $-NR^2R^3$;
und wenn R oder $R^1 = NR^2R^3$ und R^2 = Methyl oder Ethyl; dann R^3 = Methyl oder Ethyl,
und wenn R oder $R^1 = -NR^2R^3$ und R^2 = Wasserstoff, dann wird R^3 ausgewählt aus $R^4(CH_2)_nCO-$ oder R^4SO_2-;
worin wenn $R^3 = R^4(CH_2)_nCO-$ und n = 0,
R^4 ausgewählt wird aus Wasserstoff; Methyl; Ethyl; einer heterocyclischen Gruppe, ausgewählt aus einem fünfgliedrigen aromatischen oder gesättigten Ring mit einem N-, O- oder S-Heteroatom, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyridoring:



Z = N, O oder S
oder einem fünfgliedrigen aromatischen Ring mit zwei N-, O- oder S-Heteroatomen, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyridoring:

Z oder Z^1 = N, O oder S
(C_1-C_4)-Alkoxy-Gruppe;
C_6-Aryloxy-Gruppe, ausgewählt aus Phenoxy oder substituiertem Phenoxy (Substitution ausgewählt aus Halogen und (C_1-C_4)-Alkyl); oder
(C_7-C_{10})-Aralkyloxy-Gruppe;
und wenn $R^3 = R^4(CH_2)_nCO-$ und n = 1-4, R^4 ausgewählt wird aus Wasserstoff; Methyl; Ethyl; Phenyl, α-Naph-

thyl oder β-Naphthyl;
und wenn $R^3 = R^4SO_2$- und n = 0, R^4 ausgewählt wird aus Methyl, Ethyl, Phenyl, α-Naphthyl oder β-Naphthyl;

und die pharmakologisch annehmbaren organischen und anorganischen Salze oder Metallkomplexe.

4. Verbindung gemäß Anspruch 1, welche eine der folgenden ist:

[4S-(4α,12aα)]-8-Chlor-4,7-bis(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-sulfat (1:1);
[Formel I, worin R = -N(CH$_3$)$_2$, X = Cl, R^1 = -NR^{2}R^3, worin R^2 = H und R^3 für $R^4(CH_2)_nCO$ steht, worin n = 0 und R^4 = H]

[4*S*-(4α,12aα)]-9-Amino-8-chlor-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-sulfat;
[Formel I, worin R = -N(CH$_3$)$_2$, X = Cl, R^1 = -NH$_2$]

[4S-(4α,12aα)]-7-Amino-8-chlor-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-iod-1,11-dioxo-2-naphthacencarboxamid-sulfat (1:1);
[Formel I, worin R = -NH$_2$, X = Cl, R^1 = I]

[4S-(4α,12aα)]-9-Amino-8-chlor-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamidsulfat;
[Formel III, worin R = -N(Et)$_2$, X = Cl, R^1 = -NH$_2$]

[4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-8-fluor-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamidhydrochlorid;
[Formel I, worin R = N(CH$_3$)$_2$, X = F, R^1 = -NH$_2$]

[6aS-(6aα,10α)]-3-Amino-8-(aminocarbonyl)-1,10-bis(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-2-naphthacenylester-trifluormethansulfonsäure;
[Formel I, worin R = N(CH$_3$)$_2$, X = -O-SO$_2$CF$_3$, R^1 = NH$_2$]

[4S-(4α,12aα)]-8-Chlor-7-(diethylamino)-4-(dimethylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-sulfat;
[Formel I, worin R = -N(Et)$_2$, X = Cl, R^1 = -NR^{2}R^3, worin R^2 für H steht und R^3 = $R^4(CH_2)_nCO$, worin n für 0 steht und R^4 für H steht]

[4S-(4α,12aα)]-9-Amino-8-brom-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamidhydrobromid;
[Formel I, worin R = -N(CH$_3$)$_2$, X = Br, R^1 = -NH$_2$]
oder

[4S-(4α,12aα)]-9-Amino-4,7-bis(dimethylamino)-8-iod-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-hydroiodid;
[Formel I, worin R = -N(CH$_3$)$_2$, X = I, R^1 = -NH$_2$]

5. Verbindung gemäß Anspruch 2, welche eine der folgenden ist:

[4S-(4α,12aα)]-9-Azido-7-bis(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-hydrochlorid (1:1);
[Formel III, worin R = -N(CH$_3$)$_2$, X = H, R^1 = -NH$_3$]

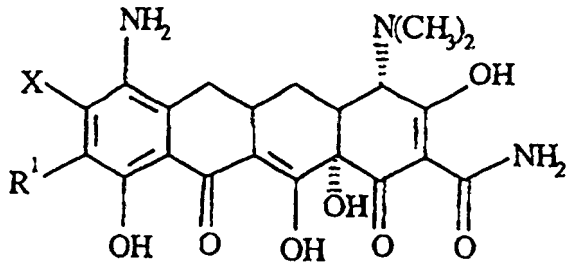
[4S-(4α,12aα)]-9-Azido-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-disulfat;
[Formel III, worin R = -N(Et)$_2$, X = H, R^1 = -NH$_3$]

[4S-(4α,12aα)]-9-Azido-7-(diethylamino)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-dihydrochlorid;

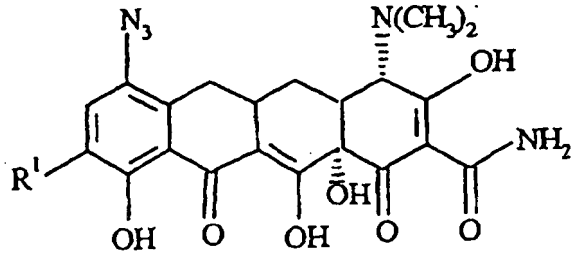
[Formel III, worin R = -N(Et)$_2$, X = H, R^1 = -NH$_3$]
oder

[4S-(4α,12aα)]-7-Azido-4-(dimethylamino)-1,4,4a,5,5a,6,-11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-iod-1,11-dioxo-2-naphthacencarboxamid-sulfat (1:1);
[Formel IV, worin R = -N$_3$, X = H, R^1 = I]

6. Verfahren zum Herstellen einer Verbindung der Formel:

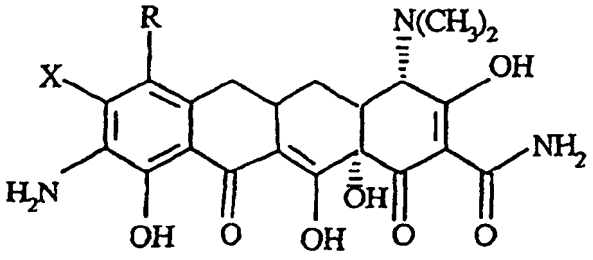


worin X und R^1 wie in Anspruch 1 definiert sind;
welches umfasst: Umsetzen einer Verbindung der Formel:

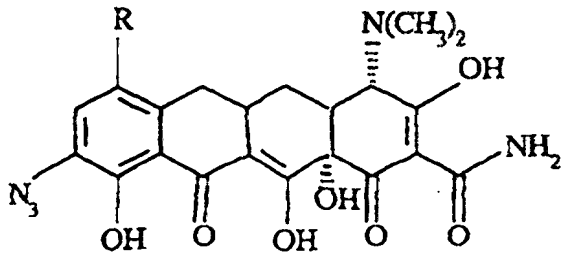


mit einer starken Säure mit der Formel HX, wenn X = Halogen oder Trifluormethansulfonyloxy, um die gewünschte Verbindung zu erhalten.

7. Verfahren zum Herstellen einer Verbindung der Formel:

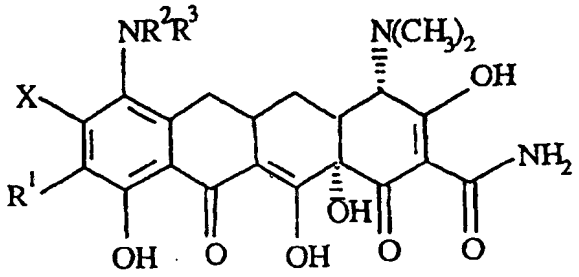


worin X und R wie in Anspruch 1 definiert sind;
welches umfasst: Umsetzen einer Verbindung der Formel:

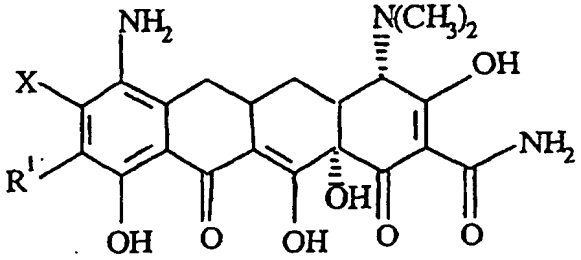


mit einer starken Säure mit der Formel HX, wenn X = Halogen oder Trifluormethansulfonyloxy, um die gewünschte Verbindung zu erhalten.

8. Verfahren zum Herstellen einer Verbindung der Formel:

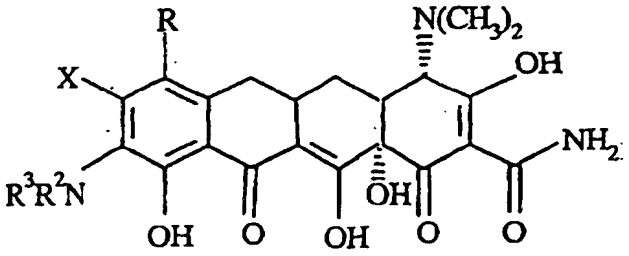


worin X, R^1, R^2 und R^3 wie in Anspruch 1 definiert sind; welches umfasst: Umsetzen einer Verbindung der Formel:

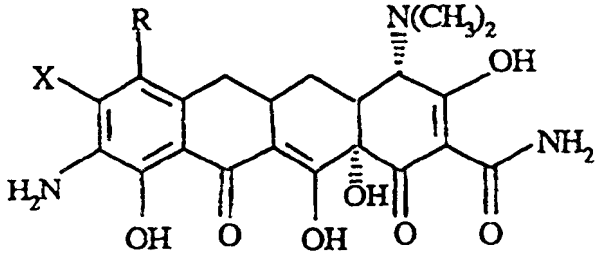


mit einem Acylhalogenid der Formel R^3-Halogenid, einem Acylanhydrid der Formel R^3-Anhydrid, einem gemischten Acylanhydrid der Formel R^3-Anhydrid, einem Sulfonylhalogenid der Formel R^3-Halogenid oder Sulfonylanhydrid der Formel R^3-Anhydrid, um die gewünschte Verbindung zu erhalten.

9. Verfahren zum Herstellen einer Verbindung der Formel:



worin X, R, R^2 und R^3 wie in Anspruch 1 definiert sind; welches umfasst: Umsetzen einer Verbindung der Formel:



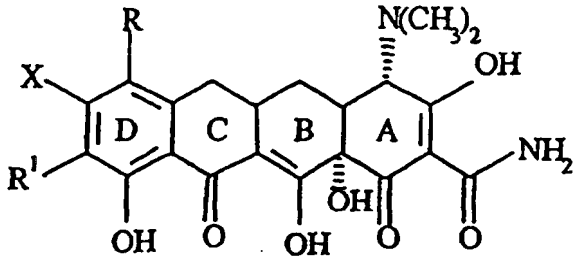
mit einem Acylhalogenid der Formel R^3-Halogenid, einem Acylanhydrid der Formel R^3-Anhydrid, einem gemischten Acylanhydrid der Formel R^3-Anhydrid, einem Sulfonylhalogenid der Formel R^3-Halogenid oder Sulfonylanhydrid der Formel R^3-Anhydrid, um die gewünschte Verbindung zu erhalten.

10. Verwendung einer Verbindung der Formel I oder II, wie in Anspruch 1 oder Anspruch 4 beansprucht, bei der Herstellung einer Arznei zur Verhinderung, Behandlung oder Bekämpfung von bakteriellen Infektionen in warmblütigen Tieren.

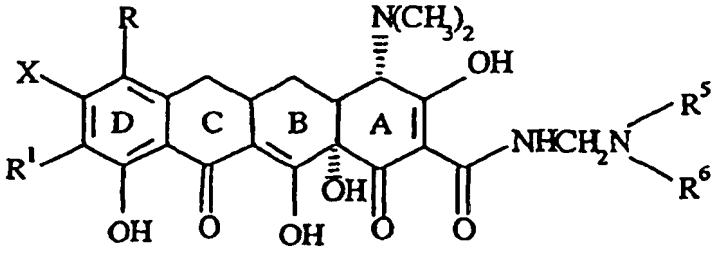
11. Pharmazeutische Zusammensetzung, welche eine Verbindung gemäß Anspruch 1 oder Anspruch 4 in Verbindung mit einem pharmazeutisch annehmbaren Träger umfasst.

Revendications

1. Composé de formule I ou II :



I

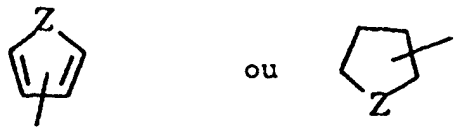


II

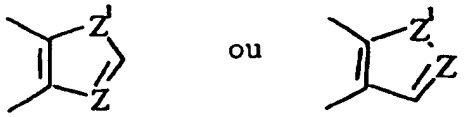
dans lesquelles :

X est sélectionné parmi un trifluorométhylsulfonyloxy, un iode, un brome, un chlore et un fluor;
R et R^1 sont identiques ou différents et sont sélectionnés parmi un amino, un chlore, un brome, un fluor, un iode, et $-NR^2R^3$;
et lorsque R ou $R^1 = NR^2R^3$ et R^2 = un méthyle ou un éthyle, alors R^3 = un méthyle ou un éthyle,
et lorsque R ou $R^1 = -NR^2R^3$ et R^2 = un hydrogène, alors R^3 est sélectionné parmi $R^4(CH_2)_nCO-$ ou $R^{4'}SO_2-$;
où lorsque $R^3 = R^4(CH_2)_nCO-$ et n = 0,

R^4 est sélectionné parmi un hydrogène, un méthyle, un éthyle, un groupement hétérocyclique sélectionné parmi un cycle aromatique ou saturé à cinq chaînons avec un hétéroatome N, O ou S



Z = N, O ou S
ou un cycle aromatique à cinq chaînons avec deux hétéroatomes N, O ou S présentant facultativement un cycle benzo ou pyrido fusionné à celui-ci



Z ou Z^1 = N, O ou S
un groupement alcoxy en C_1-C_4;
un groupement aryloxy en C_6 sélectionné parmi un phénoxy ou un phénoxy substitué (une substitution sélectionnée parmi un halogéno et un alkyle en C_1-C_4);
un groupement aralkyloxy en C_7-C_{10};
un α-aminométhoxycarbonyle;
ou
un halogénométhoxycarbonyle;

et lorsque $R^3 = R^4(CH_2)_nCO-$ et n = 1-4,

R^4 est sélectionné parmi un hydrogène; un méthyle, un éthyle; un phényle, un α-naphtyle ou un β-naphtyle;

et lorsque $R^3 = R^{4'}SO_2-$

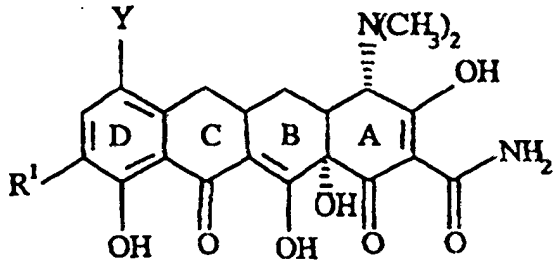
$R^{4'}$ est sélectionné parmi un méthyle, un éthyle; un phényle, un α-naphtyle ou un β-naphtyle;

R^5 est sélectionné parmi un hydrogène, un méthyle, un éthyle, un n-propyle ou un 1-méthyléthyle;
R^6 est sélectionné parmi un hydrogène, un méthyle, un éthyle, un n-propyle ou un 1-méthyléthyle;
à condition que R^5 et R^6 ne peuvent pas être tous deux un hydrogène;
ou R^5 et R^6 pris ensemble forment

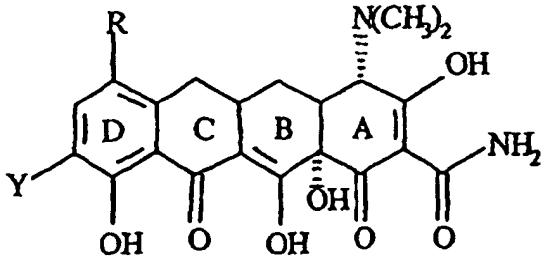
(i) $-(CH_2)_2W(CH_2)_2-$, dans laquelle W est sélectionné parmi $(CH_2)_n$ et
n = 0-1, -NH, -N(alkyle en C_1-C_3) [linéaire ou ramifié], -N(alcoxy en C_1-C_4), un oxygène et un soufre;
ou
(ii) des congénères substitués sélectionnés parmi une (L ou D)-proline et un éthyl-(L ou D)-prolinate;

et des sels organiques et inorganiques pharmaceutiquement acceptables ou des complexes métalliques.

2. Composé de formule III ou IV :



III

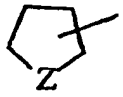


IV

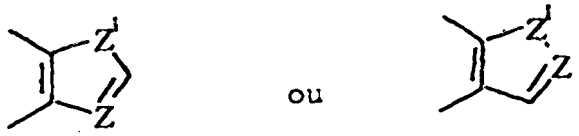
dans lesquelles Y est $-N_3$;
R et R^1 sont sélectionnés parmi un nitro; un amino; un chlore; un brome; un fluor; un iode; un cyano; un hydroxy et $-NR^2R^3$;
et lorsque R ou R^1 = $-NR^2R^3$ et R^2 = un méthyle ou un éthyle, alors R^3 = un méthyle ou un éthyle,
et lorsque R ou R^1 = $-NR^2R^3$ et R^2 = un hydrogène; alors R^3 est sélectionné parmi $R^4(CH_2)_nCO-$ ou R^4SO_2-;
où lorsque R^3 = $R^4(CH_2)_nCO-$ et n = O,

R^4 est sélectionné parmi un hydrogène; un méthyle, un éthyle; un groupement hétérocyclique sélectionné parmi un cycle aromatique ou saturé à cinq chaînons avec un hétéroatome N, O ou S présentant facultativement un cycle benzo ou pyrido fusionné à celui-ci

ou



Z = N, O ou S
ou un cycle aromatique à cinq chaînons avec deux hétéroatomes N, O ou S présentant facultativement un cycle benzo ou pyrido fusionné à celui-ci :



Z ou Z^1 = N, O ou S

un groupement alcoxy en C_1-C_4;
un groupement aryloxy en C_6 sélectionné parmi un phénoxy ou un phénoxy substitué (une substitution sélectionnée parmi un halogéno, un alkyle en C_1-C_4); ou
un groupement aralkyloxy en C_7-C_{10};

et lorsque R^3 = $R^4(CH_2)_nCO$- et n = 1-4,

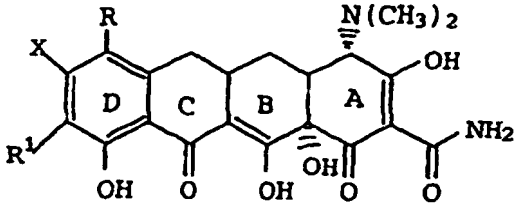
R^4 est sélectionné parmi un hydrogène; un méthyle; un éthyle; un phényle, un α-naphtyle ou un β-naphtyle;

et lorsque R^3 = $R^{4'}SO_2$-

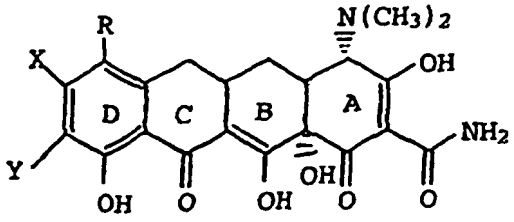
$R^{4'}$ est sélectionné parmi un méthyle, un éthyle, un phényle, un α-naphtyle ou un β-naphtyle;

et des sels organiques et inorganiques pharmaceutiquement acceptables ou des complexes métalliques.

3. Composé de formule V ou VI :



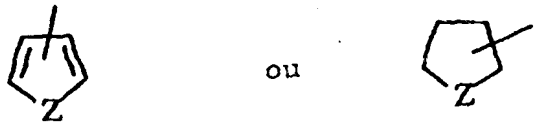
V



VI

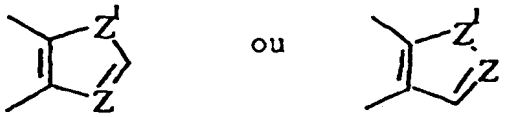
dans laquelle X est sélectionné parmi un trifluorométhylsulfonyloxy; un brome; un chlore; un fluor et un iode;
Y est sélectionné parmi $-N_2^+Cl^-$ ou $-N_3$;
R et R^1 sont sélectionnés parmi un nitro; un amino; un chlore; un brome; un fluor; un iode; un cyano; un hydroxy et $-NR^2R^3$;
et lorsque R ou R^1 = $-NR^2R^3$ et R^2 = un méthyle ou un éthyle; alors R^3 = un méthyle ou un éthyle,
et lorsque R ou R^1 = $-NR^2R^3$ et R^2 = un hydrogène; alors R^3 est sélectionné parmi $R^4(CH_2)_nCO$- ou $R^{4'}SO_2$-;
où lorsque R^3 = $R^4(CH_2)_nCO$- et n = 0.

R^4 est sélectionné parmi un hydrogène; un méthyle, un éthyle; un groupement hétérocyclique sélectionné parmi un cycle aromatique ou saturé à cinq chaînons avec un hétéroatome N, O ou S présentant facultativement un cycle benzo ou pyrido fusionné à celui-ci :



Z = N, O ou S

ou un cycle aromatique à cinq chaînons avec deux hétéroatomes N, O ou S présentant facultativement un cycle benzo ou pyrido fusionné à celui-ci :



Z ou Z^1 = N, O ou S

un groupement alcoxy en C_1-C_4;
un groupement aryloxy en C_6 sélectionné parmi un phénoxy ou un phénoxy substitué (une substitution sélectionnée parmi un halogéno, un alkyle en C_1-C_4); ou
un groupement aralkyloxy en C_7-C_{10};

et lorsque $R^3 = R^4(CH_2)_nCO$- et n = 1-4,

R^4 est sélectionné parmi un hydrogène; un méthyle, un éthyle; un phényle, un α-naphtyle ou un β-naphtyle;

et lorsque $R^3 = R^{4'}SO_2$- et n = 0,

$R^{4'}$ est sélectionné parmi un méthyle, un éthyle; un phényle, un α-naphtyle ou un β-naphtyle;

et des sels organiques et inorganiques pharmaceutiquement acceptables ou des complexes métalliques.

4. Composé suivant la revendication 1, qui est un des suivants :

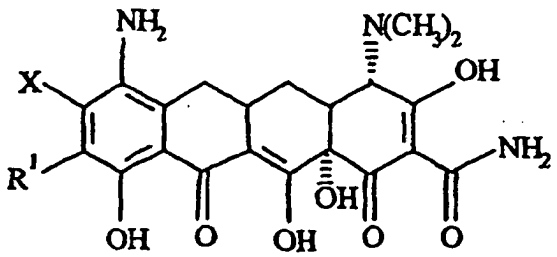
le sulfate de [4S-(4α,12aα)]-8-chloro-4,7-bis(diméthylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide (1:1);
[Formule I dans laquelle R = -N(CH$_3$)$_2$, X = Cl, R^1 = -NR^{2}R^3 où R^2 = H et R^3 est R^4(CH$_2$)$_n$CO où n = 0 et R^4 = H]
le sulfate de [4S-(4α,12aα)]-9-amino-8-chloro-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide;
[Formule I dans laquelle R = -N(CH$_3$)$_2$, X = Cl, R^1 = -NH$_2$]
le sulfate de [4S-(4α,12aα)]-7-amino-8-chloro-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-iodo-1,11-dioxo-2-naphtacènecarboxamide (1:1);
[Formule I dans laquelle R = -NH$_2$, X = Cl, R^1 = I]
le sulfate de [4S-(4α,12aα)]-9-amino-8-chloro-7-(diéthylamino)-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide;
[Formule III dans laquelle R = -N(Et)$_2$, X = Cl, R^1 = NH$_2$]
l'hydrochlorure de [4S-(4α,12aα)]-9-amino-4,7-bis(diméthylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide;
[Formule I dans laquelle R = N(CH$_3$)$_2$, X = F, R^1 = NH$_2$]
l'ester d'acide trifluorométhanesulfonique [6aS-(6aα,10α)]-3-amino-8-(aminocarbonyl)-1,10-bis(diméthylami-

no)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tétrahydroxy-5,7-dioxo-2-naphtacényle:
[Formule I dans laquelle R = $N(CH_3)_2$, X = $O\text{-}SO_2CF_3$, $R^1 = NH_2$]
le sulfate de [4S-(4α,12aα)]-8-chloro-7-(diéthylamino)-4-(diméthylamino)-9-(formylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide;
[Formule I dans laquelle R = $-N(Et)_2$, X = Cl, $R^1 = -NR^2R^3$ où R^2 est H et $R^3 = R^4(CH_2)_nCO$ où n est 0 et R^4 est H]
l'hydrobromure de [4S-(4α,12aα)]-9-amino-8-bromo-4,7-bis (diméthylamino) -1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide;
[Formule I dans laquelle R = $-N(CH_3)_2$, X = Br, $R^1 = -NH_2$]
ou
l'hydroiodure de [4S-(4α,12aα)]-9-amino-4,7-bis(diméthylamino)-8-iodo-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide;
[Formule I dans laquelle R = $-N(CH_3)_2$, X = I, $R^1 = -NH_2$]

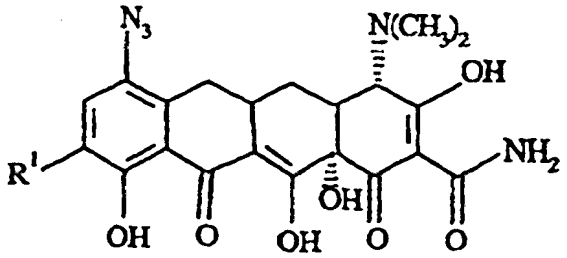
5. Composé suivant la revendication 2, qui est un des suivants :

l'hydrochlorure de [4S-(4α,12aα)]-9-azido-7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide (1:1);
[Formule III dans laquelle R = $-N(CH_3)_2$, X = H, $R^1 = -N_3$]
le disulfate de [4S-(4α,12aα)]-9-azido-7-(diéthylamino)-4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide;
[Formule III dans laquelle R = $-N(Et)_2$, X = H, $R^1 = N_3$]
le dihydrochlorure de [4S-(4α,12aα)]-9-azido-7-(diéthylamino) -4-(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide (1:1);
[Formule III dans laquelle R = $-N(Et)_2$, X = H, $R^1 = N_3$]
ou
le sulfate de [4S-(4α,12aα)-7-azido-4-(diméthylamino)-1,4, 4a, 5,5a,6, 11, 12a-octahydro-3, 10, 12, 12a-tétrahydroxy-9-iodo-1,11-dioxo-2-naphtacènecarboxamide (1:1);
[Formule IV dans laquelle R = $-N_3$, X = H, R^1 = I]

6. Procédé de production d'un composé de formule :

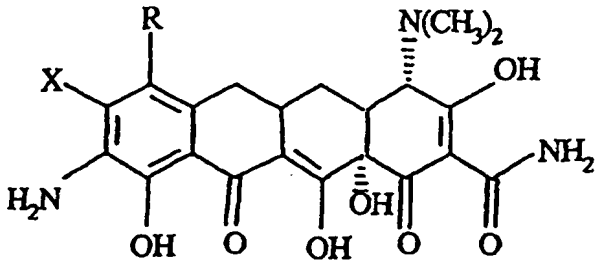


dans laquelle X et R^1 sont comme définis à la revendication 1;
qui comprend la réaction d'un composé de formule :

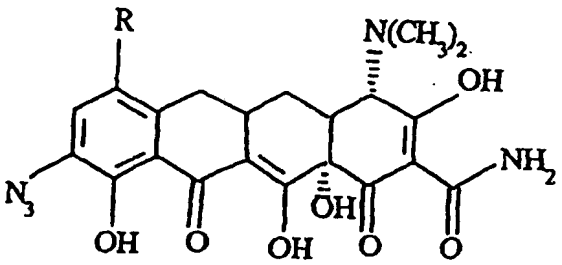


avec un acide fort de formule HX lorsque X = un halogène ou un trifluorométhanesulfonyloxy, pour obtenir le composé souhaité.

7. Procédé de production d'un composé de formule :

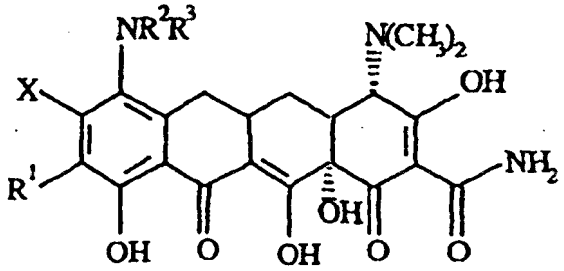


dans laquelle X et R sont comme définis à la revendication 1;
qui comprend la réaction d'un composé de formule :

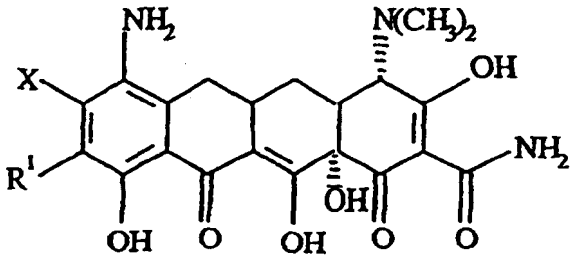


avec un acide fort présentant la formule HX lorsque X = un halogène ou un trifluorométhanesulfonyloxy, pour obtenir le composé souhaité.

8. Procédé de production d'un composé de formule :

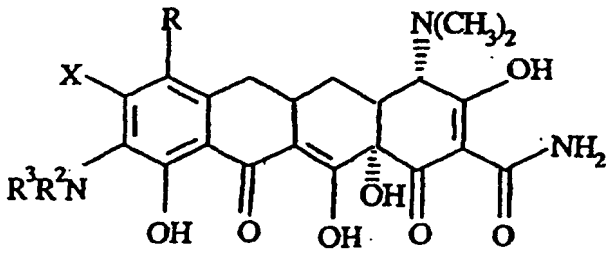


dans laquelle X, R^1, R^2 et R^3 sont comme définis à la revendication 1; qui comprend la réaction d'un composé de formule :

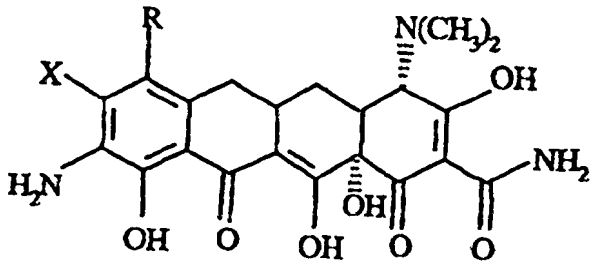


avec un halogénure d'acyle de formule R^3-halogénure, un anhydride d'acyle de formule R^3-anhydride, un anhydride d'acyle mixte de formule R^3-anhydride, un halogénure de sulfonyle de formule R^3-halogénure ou un anhydride de sulfonyle de formule R^3-anhydride pour obtenir le composé souhaité.

9. Procédé de production d'un composé de formule :



dans laquelle X, R, R^2 et R^3 sont comme définis à la revendication 1;
qui comprend la réaction d'un composé de formule :



avec un halogénure d'acyle de formule R^3-halogénure, un anhydride d'acyle de formule R^3-anhydride, un anhydride d'acyle mixte de formule R^3-anhydride, un halogénure de sulfonyle de formule R^3-halogénure ou un anhydride de sulfonyle de formule R^3-anhydride pour obtenir le composé souhaité.

10. Utilisation d'un composé de formule I ou II suivant la revendication 1 ou la revendication 4, dans la préparation d'un médicament pour la prévention, le traitement ou le contrôle d'infections bactériennes chez des animaux à sang chaud.

11. Composition pharmaceutique comprenant un composé suivant la revendication 1 ou la revendication 4, en association avec un vecteur pharmaceutiquement acceptable.